Myoglobin: Just an Oxygen Store or Also an Oxygen Transporter?

Klaus D. Jürgens, Simon Papadopoulos, Thomas Peters, and Gerolf Gros

Besides acting as an oxygen store during times of reduced blood oxygen supply, myoglobin can also facilitate intracellular oxygen transport by diffusion of oxymyoglobin along a PO₂ gradient. We reassess the importance of myoglobin-facilitated oxygen diffusion by applying new findings on the intracellular diffusivity of myoglobin in a model calculation.

The role of myoglobin as an oxygen store is well established. In terrestrial mammals, it compensates for the disadvantage of a reduced blood flow in heart and skeletal muscle during contraction. In aquatic mammals, which are characterized by markedly higher myoglobin concentrations than terrestrial mammals, it serves as an oxygen reservoir during the time ventilation ceases.

The physiological significance of myoglobin-facilitated oxygen diffusion, i.e., reversible combination of myoglobin with oxygen and translational diffusion of oxymyoglobin molecules, has been a matter of controversy since Wittenberg (15) first reported evidence for it. Several approaches have been used to explore the physiological importance of this mechanism of intracellular oxygen transport. It has been attempted to experimentally evaluate its role in isolated cells, in isolated muscle tissue, and in vivo, both directly by chemically or genetically abolishing myoglobin function in the cell and observing the consequences for oxygen consumption or for physical performance and indirectly by determining the oxygen conductance of muscle tissue from measurements of oxygen consumption and intracellular PO₂ gradients. Theoretically, the problem was assessed in numerous model calculations, all of which until recently suffered from the lack of a reliable value for the intracellular diffusivity of myoglobin. We summarize here the results of these studies, and, taking into account our data on the intracellular myoglobin diffusivity, reevaluate the physiological role of myoglobin-facilitated oxygen transport in heavily exercising muscles by applying a modified Krogh cylinder model (6).

Evidence for facilitated oxygen diffusion from abolishing myoglobin function

In an earlier study (12), we concluded that all experimental studies reporting evidence for a significant contribution of myoglobin-facilitated diffusion to total intracellular oxygen transport exhibit experimental insufficiencies. One group blocked myoglobin function with carbon monoxide but chose an experimental setup in which severe hypoxia or anoxia was present in the muscle tissue investigated. Therefore, these results essentially show that myoglobin-facilitated oxygen diffusion plays a role at unphysiologically low PO₂ (Table 1). Other groups used myoglobin-blocking reagents that are known to cause severe side effects (Table 1). Thus, besides the desired inhibitory effect on myoglobin, substantial poisoning effects on other proteins involved in cellular respiration cannot be excluded in these studies. Furthermore, blocking of myoglobin not only abolishes facilitated oxygen diffusion but also prevents the storage of oxygen. In rhythmically contracting muscles, the lack of an oxygen store may cause reduced performance, just as a lower oxygen conductance does. Therefore, from these experimental approaches no clear evidence can be derived that, under physiological conditions, the working muscle significantly benefits from myoglobin-facilitated oxygen diffusion.

Recently, two groups who performed a knockout of the myoglobin gene in mice have arrived at contradictory results (Table 1). Garry et al. (2) reported that myoglobin-free mice exhibit normal exercise capacity and show no striking changes in muscle tissue parameters compared with normal mice. Gödecke et al. (5) also did not observe any physical disadvantage of myoglobin-free mice but found a 30% higher capillary density of the heart and, in beating Langendorff hearts perfused with hemoglobin-free solution, a 25% higher maximal coronary blood flow. This flow may be considerably less elevated in beating myoglobin-free hearts in vivo when perfused with blood.

In these knockout mice, the lack of myoglobin has obviously induced compensatory mechanisms during ontogeny, but in our opinion it is not clear whether these mechanisms are required to compensate for the absence of the storage function of myoglobin or to compensate for a lack of myoglobin-facilitated oxygen diffusion. At a given oxygen consumption, a higher blood flow as well as a higher capillary density increases the Po₂ of the tissue and hence increases the concentration of dissolved oxygen. This additional amount of oxygen stored in the heart has been calculated to be large enough to ensure a sufficient oxygen supply during systolic cessation of blood flow in the myoglobin-free rat heart.

Evidence for facilitated oxygen diffusion from measuring intracellular MbSO₂ gradients

Indirect evidence for a substantial role of myoglobin-facilitated oxygen transport in working muscle has been
deduced from the finding of surprisingly low intracellular PO2 gradients by Gayeski and Honig (3, 4). They used a cryospectrophotometric method and reported local intracellular myoglobin oxygen saturations (MbSO2) of not more than 10–30% in heavily exercising dog gracilis muscles and intracellular PO2 values ranging between 0.5 and 3.5 mmHg throughout the cell. To explain these results, they claimed that a steep oxygen pressure drop occurs between the erythrocytes and the sarcolemma, i.e., in the so-called carrier-free (heme protein-free) layer. The resulting shallow intracellular PO2 gradient between sarcolemma and the center of the muscle fiber (as well as along the fiber axis) was assumed to be possible due to a high intracellular oxygen conductance effected by a high degree of myoglobin-facilitated oxygen diffusion, i.e., high diffusivity and/or concentration of myoglobin.

However, the statement of Gayeski and Honig that their measuring method yields local intracellular MbSO2 has recently been withdrawn by this group (14). Originally, it had been assumed that each of the recorded MbSO2 signals represents the average of an area of 20 μm², but later it was found that this area was ~500 times greater, thus covering about five muscle cell cross-sections. Therefore, their cryospectrophotometric measurements of the MbSO2 and the corresponding PO2 values do not represent local intracellular conditions but are values from a relatively large area averaged over several fibers. Consequently, these studies do not rule out the existence of large intracellular oxygen gradients between sarcolemma and mitochondria, since the average oxygen saturation must be low as long as a low oxygen saturation prevails in the bulk of the tissue. Hence, these measurements provide neither evidence for a shallow intracellular PO2 gradient nor for a significant myoglobin-facilitated oxygen diffusion.

**Evidence for facilitated oxygen diffusion from determining mean muscle tissue PO2**

It remains true that the cryospectrophotometric method leads to a relatively low mean cellular MbSO2 of 10–30% in heavily exercising leg muscle of the dog (Table 2). Noninvasive measurements in heavily working human skeletal and rat heart muscle by nuclear magnetic resonance (NMR), on the other hand, do not support such low mean muscle MbSO2. These studies report mean MbSO2 values between 49% and 73% for skeletal muscles and 76% for heart muscle (Table 2). Nevertheless, although the mean muscle MbSO2 of the NMR studies are considerably higher, the authors state that their results are in accordance with the finding of an extremely low intracellular PO2, as reported by Gayeski and Honig (8, 10, 13), and consider this as support of the idea of a high tissue oxygen conductance due to myoglobin-facilitated oxygen diffusion. A closer look reveals that the low tissue PO2 values calculated in these studies are, at least in part, due to a mathematical artifact. It has become common usage to derive the mean PO2 from the myoglobin oxygen half saturation pressure (P50) and the mean tissue MbSO2 using the equation PO2 = P50[MbSO2/(1 – MbSO2)]. This function describes the myoglobin oxygen binding curve. It should be noted that this relation is nonlinear. For example, if we consider two different sites in a muscle, one exhibiting an oxygen saturation of 0.5 and the other one of 0.97, we calculate from this equation (applying a P50 of 2.4 mmHg) corresponding PO2 values of 2.4 and 77.6 mmHg. The mean value of MbSO2 is 0.735, and the mean PO2 is 40 mmHg. If we take the mean MbSO2 value of 0.735 to calculate a mean PO2 by this equation, we arrive at a value of 6.66 mmHg, which is clearly much lower than the true mean of 40 mmHg. Because of the hyperbolic shape of the oxygen-binding curve (at a PO2 of 20 mmHg myoglobin is saturated by 90% with oxygen at

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Authors</th>
<th>Myoglobin Function Abolished By</th>
<th>Conclusion from Experiments</th>
<th>Critical Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken gizzard</td>
<td>de Koning et al. <em>Pflügers Arch</em> 389: 211–217, 1981.</td>
<td>CO</td>
<td>Significant role of myoglobin-facilitated oxygen diffusion</td>
<td>Severe hypoxia due to sample thickness</td>
</tr>
<tr>
<td>Rat heart</td>
<td>Taylor et al. <em>Respir Physiol</em> 63: 275–283, 1986.</td>
<td>Nitrite</td>
<td>Significant role of myoglobin-facilitated oxygen diffusion</td>
<td>Severe hypoxia (anoxia) due to N equilibration; nitrite can directly reduce myocardial performance</td>
</tr>
<tr>
<td>Mouse heart, m. soleus</td>
<td>Garry et al. (2)</td>
<td>Genetic knockout</td>
<td>Myoglobin not required for oxygen transport</td>
<td>No documentation of blood flow and capillary densities</td>
</tr>
<tr>
<td>Mouse heart</td>
<td>Gödecke et al. (5)</td>
<td>Genetic knockout</td>
<td>Significant role of myoglobin-facilitated oxygen diffusion likely</td>
<td>Differentiation between storage and transport function of myoglobin not possible</td>
</tr>
</tbody>
</table>

**TABLE 1. Results of experimentally abolishing myoglobin function in muscle tissue**
TABLE 2. Measured values of mean myoglobin oxygen saturation in various muscle tissues and the corresponding PO₂

<table>
<thead>
<tr>
<th>Muscle (Method)</th>
<th>MbSO₂ mean</th>
<th>PO₂ Mb mean, mmHg</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog gracilis stimulated to work</td>
<td>0.20 ± 0.04</td>
<td>1.4 ± 0.3</td>
<td>Gayeski and Honig (4)</td>
</tr>
<tr>
<td>at Vₒ₂₅₀% (Cryospectrophotometry)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human quadriceps femoris working</td>
<td>0.49 ± 0.03</td>
<td>3.1 ± 0.4</td>
<td>Richardson et al. (13)</td>
</tr>
<tr>
<td>at 50–100% of Vₒ₂₅₀ (NMR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human calf muscle at constant</td>
<td>0.73 ± 0.30</td>
<td>Not given</td>
<td>Mancini et al. Circulation</td>
</tr>
<tr>
<td>maximal and rapid incremental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise (NMR)</td>
<td>0.53 ± 0.27</td>
<td></td>
<td>90: 500–508, 1994.</td>
</tr>
<tr>
<td>Rat heart beating at 50–500 min⁻¹</td>
<td>0.76 ± 0.06</td>
<td>7.9 ± 3.0</td>
<td>Jelicks and Wittenberg (8)</td>
</tr>
</tbody>
</table>

MbSO₂ mean = mean myoglobin oxygen saturation; PO₂ Mb mean = corresponding PO₂ calculated from MbSO₂ mean; NMR, nuclear magnetic resonance.

37°C), an apparent mean tissue PO₂ derived from a mean MbSO₂ will ignore high PO₂ values and tend to be dominated by the areas of lower PO₂. As is shown by a calculation using a modified Krogh cylinder tissue model (see below), the real mean tissue PO₂ values (true mean PO₂) exceed the ones calculated by the original equation (PO₂ Mb mean) by ~100% (Table 3). Since Gayeski and Honig as well as the groups applying the NMR technique used the above equation to calculate a mean muscle tissue PO₂, their results are not valid.

A completely different picture of muscle tissue PO₂ has been given by Harrison et al. (7), who, using multiwire surface electrodes, found a mean PO₂ of 40 mmHg and practically no value below 10 mmHg in dog sartorius muscle exercising at up to 90% of Vₒ₂ max. It appears possible that this method, too, does not give a representative mean tissue PO₂, since the conditions on the surface of the muscle may be significantly different from those in its interior and produce an overestimation of the PO₂.

Consequently, at present there is no method available to experimentally obtain reliable mean PO₂ values of working muscles. Calculating mean muscle PO₂ from mean MbSO₂ leads to a systematic underestimation of the true mean PO₂. Therefore, if a mean muscle PO₂ calculated this way turns out to be low, this cannot be taken as an indication of a high intracellular oxygen conductivity due to facilitated oxygen diffusion.

**Intracellular diffusivity of myoglobin**

Since there is no convincing evidence for the role of myoglobin in intracellular oxygen transport from experimentally abolishing myoglobin function, and since no method is available to obtain local tissue MbSO₂ and PO₂ values in exercising muscle tissue, we examined the importance of myoglobin as an intracellular oxygen transporter by applying model calculations. A prerequisite to obtain meaningful results from such calculations is to employ reliable model parameters. Only recently have experimental results for the diffusion coefficient of myoglobin (Dₘb) in intact mammalian skeletal muscle fibers become available after several methods to measure this quantity were developed in our laboratory.

First, the photo-oxidation method is based on the generation of an intracellular gradient of metmyoglobin along the longitudinal cell axis (9). This gradient is achieved by irradiating a small area of a rat diaphragm muscle with an ultraviolet light pulse with the use of a microscope photometer. In this area, the ultraviolet light oxidizes ~10% of the native oxymyoglobin to metmyoglobin. The subsequent diffusion of metmyoglobin out of and of oxymyoglobin into this area is followed photometrically in the center of the irradiated field at a wavelength of 420 nm. At this wavelength, the absorbance coefficients of oxy- and metmyoglobin are markedly different, so that changes of the concentration ratio of the two myoglobin species lead to significant changes in absorbance. Minor ultraviolet side effects on tissue components other than myoglobin, which influence the absorbance change at 420 nm, are eliminated by subtracting simultaneously recorded absorbance changes at 473 nm, which is an isosbestic wavelength for oxy- and metmyoglobin.

The recovery of oxymyoglobin in the irradiated field is described by a differential equation, and the value of Dₘb is determined by fitting the numerical solution of this equation to the measured kinetics. The axial diffusion coefficient of myoglobin at 22°C obtained by the photo-oxidation method in rat diaphragm muscle amounts to (1.17 ± 0.08) × 10⁻⁷ cm²/s (mean ± SE).

Second, to validate this finding we determined Dₘb with another method. The injection method (12) is based on the injection of a minute amount of metmyoglobin (~30 pl) under microscopic control into a single muscle cell of a fiber bundle of a rat soleus muscle with a pneumatic picopump. The profiles of the generated metmyoglobin concentration gradients along the longitudinal fiber axis are recorded photometrically at a wavelength of 410 nm by using a scanning stage. The recordings are repeated in defined time intervals, and the diffusion coefficients are calculated by fitting the numerical solution of the underlying differential equation to the curves measured at different times. The microinjection method led to an axial Dₘb of (1.25 ± 0.13) × 10⁻⁷ cm²/s in rat soleus muscle at 22°C. This value is not significantly different from the value obtained by the photo-oxidation technique for the diaphragm muscle, which like the soleus of the rat predominantly consists of myoglobin-rich fibers. With the injection method, we also performed measurements at 37°C and found a Dₘb of (2.20 ± 0.12) × 10⁻⁷ cm²/s. From the temperature dependence of Dₘb, a temperature coefficient (Q₁₀) of 1.46 can be calculated.
Our experimental results reveal that the mobility of myoglobin in the sarcoplasm is much lower than observed in concentrated myoglobin solutions. The highly ordered cytoskeletal structure of the muscle cell seems to reduce protein diffusivity, in comparison to that in water, three times more than do the viscosity effects exerted by a protein solution of a concentration of 24 g/dl, which represents the total protein concentration of a muscle cell.

Evidence for facilitated oxygen diffusion from model calculations with experimental $D_{mb}$

For the human quadriceps femoris muscle, we calculated the local distribution of MbSO2 and PO2, as well as the contribution of myoglobin-facilitated oxygen diffusion to total oxygen diffusion, $V_{O2\text{Mb}}/V_{O2\text{tot}}$, by using a muscle tissue model. We chose the modified Krogh cylinder model and the corresponding set of equations given by Groebe (6). This model consists of three concentric cylinders, the inner one representing the interior of the capillary, the middle one extending from the surface of the red blood cell to the sarcolemma (the "carrier-free" region), and the outer one representing the myoglobin-containing muscle tissue supplied by the central capillary. The data required to model the human quadriceps femoris muscle are given in the legend of Fig. 1.

Since the intraerythrocytic oxygen pressure drop included in Groebe's model amounts to only 1–3 mmHg when our set of parameters is used, we neglected this feature of Groebe's model. We performed calculations for $D_{mb} = 0$, i.e., immobile myoglobin, for $D_{mb} = 2.2 \times 10^{-7}$ cm$^2$/s, the value measured by us, and for $D_{mb} = 8 \times 10^{-7}$ cm$^2$/s, the relatively high diffusivity often used previously in model calculations.

For the calculations, it was assumed that the peripheral PO2 on the venous side of the cylinder is zero, i.e., that neither a significant anoxic region nor an excess supply of oxygen occurs in the cylinder. For a given set of parameters, this was achieved by adequately adjusting the capillary blood flow ($Q_c$).

Figure 1 shows the results of the model calculation for a $D_{mb}$ of 2.2 $\times 10^{-7}$ cm$^2$/s at an oxygen consumption of 150 ml O2·kg$^{-1}$·min$^{-1}$ and an arterial hemoglobin saturation of 95%. Shown are the PO2 field (Fig. 1A), the MbSO2 field (Fig. 1B), and the field of the fractional myoglobin-facilitated oxygen transport ($V_{O2\text{Mb}}/V_{O2\text{tot}}$) (Fig. 1C) within the cylinder. The PO2 values fall continuously from the arterial to the venous end and from the center to the periphery of the cylinder, whereas the myoglobin remains essentially saturated with oxygen over almost half of the total cylinder volume. In this part of

### Table 3. Results of Krogh model calculations for the heavily working human quadriceps femoris muscle for three different diffusion coefficients of myoglobin

<table>
<thead>
<tr>
<th>$D_{mb}$, $10^{-7}$ cm$^2$/s</th>
<th>MbSO2 mean</th>
<th>True PO2 mean, mmHg</th>
<th>PO2 Mb mean, mmHg</th>
<th>Mean $V_{O2\text{Mb}}/V_{O2\text{tot}}$, %</th>
<th>PO2r, mmHg</th>
<th>$Q_c$, ml·kg$^{-1}$·min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.82</td>
<td>22</td>
<td>14.3</td>
<td>0</td>
<td>28.2</td>
<td>1380</td>
</tr>
<tr>
<td>2.2</td>
<td>0.78</td>
<td>20</td>
<td>11.4</td>
<td>3.9</td>
<td>24.8</td>
<td>1200</td>
</tr>
<tr>
<td>8</td>
<td>0.73</td>
<td>17</td>
<td>8.6</td>
<td>16.0</td>
<td>17.0</td>
<td>940</td>
</tr>
</tbody>
</table>

Applying this $Q_c$ to the value obtained by the ultraviolet method leads to a value of $2.1 \times 10^{-7}$ cm$^2$/s at $37^\circ$C.

Third, it has been argued that the axial myoglobin diffusion coefficient, which we measured with these two methods, may be different from the physiologically more relevant radial diffusion coefficient. Therefore, a third method was developed (Papadopoulos et al., unpublished methods). Fluorescently labeled myoglobin is injected at two neighboring sites into a rat soleus muscle fiber and allowed to spread over the fiber until a homogeneous distribution of the injected protein is reached between the injection sites, so that no axial concentration gradient is present. Then the myoglobin in the central part of the muscle fiber cross-section is photobleached with a pulse of an argon ion laser, thus generating a radial gradient of fluorescence between the center and the periphery of the fiber. The fluorescence recovery after photobleaching (FRAP) due to radial myoglobin diffusion is subsequently recorded in the bleached area, and the numerical solution of the diffusion equation is fitted to the observed kinetics. At $22^\circ$C, the resulting $D_{mb}$ was $(1.22 \pm 0.05) \times 10^{-7}$ cm$^2$/s, which is not significantly different from the values obtained for the axial diffusion coefficients. This leads to the conclusion that there is no anisotropy of myoglobin diffusion in skeletal muscle fibers. The same holds for heart muscle. In rat cardiomyocytes we estimated nearly identical values, $(1.17 \pm 0.07) \times 10^{-7}$ and $(1.25 \pm 0.08) \times 10^{-7}$ cm$^2$/s, respectively, for the axial and the radial diffusion coefficients of myoglobin with the FRAP method. These values are also not significantly different from the values found in skeletal muscle.

Our results for $D_{mb}$ are in good agreement with two earlier experimental results. Baylor and Pape (1) reported a value of $1.6 \times 10^{-7}$ cm$^2$/s ($22^\circ$C) for the diffusivity of myoglobin in frog skeletal muscle, which is normally free of myoglobin. Moll (11) obtained a value of $1.5 \times 10^{-7}$ cm$^2$/s at $20^\circ$C and $2.7 \times 10^{-7}$ cm$^2$/s at $37^\circ$C in undiluted homogenates of rat skeletal muscles.

A review of the literature, however, shows that during the last 20 years $D_{mb}$ values ranging from $5 \times 10^{-7}$ to $23 \times 10^{-7}$ cm$^2$/s ($37^\circ$C), i.e., values that are 2–10 times greater than the value obtained experimentally, were applied in model calculations of the contribution of myoglobin-facilitated oxygen diffusion to tissue oxygen transport. As a consequence, the contribution of myoglobin-facilitated oxygen diffusion has been considerably overestimated in most theoretical studies.

In many of these studies, a $D_{mb}$ value of $8 \times 10^{-7}$ cm$^2$/s, the result obtained from measurements of the myoglobin self diffusion in 18 g/dl myoglobin solution, has been used.
the cylinder, facilitated oxygen diffusion is negligible. A significant contribution of myoglobin-facilitated oxygen diffusion to tissue oxygen transport can take place only in approximately one-third of the cylinder volume because only there, at the venous end, do significant oxymyoglobin gradients occur. Averaged over the whole tissue cylinder, myoglobin-facilitated oxygen diffusion contributes only little to total oxygen diffusion and amounts to no more than 4% when calculated with the $D_{Mb}$ measured by us, compared with 16% when calculated with $D_{Mb} = 8 \times 10^{-7}$ cm$^2$/s, the value often used in the literature (Table 3). To cover the given oxygen consumption of the tissue, the end-capillary $P_{O_2}$ ($P_{O_2c}$) can be 3.4 mmHg smaller at a $D_{Mb}$ of $2.2 \times 10^{-7}$ cm$^2$/s compared with the state when myoglobin is immobile ($D_{Mb} = 0$). The lower $P_{O_2c}$ is associated with a reduction in $Q$ of 13% in this muscle and, hence, a somewhat lower cardiac output. This economic benefit is small compared with a 32% lower tissue perfusion rate at a 11.2 mmHg smaller $P_{O_2c}$ estimated for a high $D_{Mb}$ of $8 \times 10^{-7}$ cm$^2$/s (Table 3). Our results indicate that because of the relatively low intracellular diffusivity of myoglobin, facilitated oxygen diffusion is of minor importance for oxygen transport in heavily exercising skeletal muscle under physiological conditions.

We furthermore used our model to estimate mean $MbO_2$ and mean $P_O_2$ of muscle tissue. Table 3 shows that the mean $MbO_2$ is relatively high (0.82) when the myoglobin is immobile.
But also in the presence of facilitated oxygen diffusion with the diffusion coefficient of myoglobin, the mean measured MbSO$_2$ is reduced only slightly to 0.78, and it remains as high as 0.73 even when the four-times-higher myoglobin diffusivity of $8 \times 10^{-7}$ cm$^2$/s is used. These values are in accordance with the upper limit of MbSO$_2$ values measured by NMR techniques in heavily working skeletal and heart muscles, but they are considerably higher than the result obtained by Honig and Gayeski (Table 2).

The true mean PO$_2$ within the myoglobin-containing muscle tissue also fall only slightly with increasing diffusivity of myoglobin and range between 22 and 17 mmHg (Table 3). These model PO$_2$ values, however, are considerably higher than many values reported in the literature (PO$_2$.Mb-mean in Table 2), which are systematically underestimated due to their erroneous calculation by use of the myoglobin oxygen binding curve (see above).

It may be noted that we find that the pressure drop in the carrier-free layer hardly affects the mean tissue PO$_2$. If this region is included in the calculation of the true mean PO$_2$, the values given in Table 3 increase by <0.5 mmHg.

Our data show that the low myoglobin diffusivity as measured by us is compatible with the mean MbSO$_2$ values obtained experimentally by NMR and that these oxygen saturations are also compatible with mean tissue PO$_2$ values that are much higher than has often been postulated (Table 2).

The main findings of this review of the role of myoglobin in oxygen transport in skeletal muscle of terrestrial mammals can be summarized as follows:

- There is no unequivocal evidence for a significant physiological role of myoglobin-facilitated oxygen diffusion from experiments in which myoglobin was chemically blocked or genetically knocked out.
- At present, there are no local measurements of intracellular myoglobin oxygen saturations and there is no experimental evidence for shallow intracellular PO$_2$ gradients in muscle tissue. Thus there is no evidence for a particularly high intracellular oxygen conductivity.
- Calculation of the mean tissue PO$_2$ from a mean MbSO$_2$ by the equation describing the oxygen binding curve of myoglobin leads to a considerable systematic underestimation of the true mean PO$_2$.
- The directly measured diffusivity of myoglobin in skeletal muscle cells is 2–10 times lower than previously assumed. Therefore, in previous model calculations the extent of myoglobin-facilitated diffusion has been overestimated.
- New calculations of PO$_2$ profiles and the magnitude of facilitated compared with free oxygen diffusion using a Krogh cylinder model reveal that the role of myoglobin as an oxygen transporter is of minor significance under physiological conditions.

We would like to dedicate this article to Prof. Heinz Bartels on the occasion of his 80th birthday.

References


Editor’s Note

In a letter commenting on the article by M. I. Philips and K. M. Schmidt-Ott (The Discovery of Renin 100 Years Ago. News Physiol Sci 14: 271–275, 1999), Dr. Morton H. Frank of Philadelphia has pointed out that an earlier translation than that of Philips and Schmidt-Ott may be attributed to A. Ruskin (Classics in Arterial Hypertension. Springfield, IL: Charles C. Thomas, 1956, p. 274–287) and that it was Poiseuille, not Carl Ludwig, who invented the mercury manometer.

We are grateful to Dr. Frank for his corrections.

The Editors