Estimating oxygen transport resistance of the microvascular wall

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Vadapalli, Arjun, Roland N. Pittman, and Aleksander S. Popel. Estimating oxygen transport resistance of the microvascular wall. Am J Physiol Heart Circ Physiol 279: 657–671, 2000.—The problem of diffusion of O2 across the endothelial surface in precapillary vessels and its utilization in the vascular wall remains unresolved. To establish a relationship between precapillary release of O2 and vascular wall consumption, we estimated the intravascular flux of O2 on the basis of published in vivo measurements. To interpret the data, we utilized a diffusion model of the vascular wall and computed possible physiological ranges for O2 consumption. We found that many flux values were not consistent with the diffusion model. We estimated the mitochondrial-based maximum O2 consumption of the vascular wall (Mmt) and a possible contribution to O2 consumption of nitric oxide production by endothelial cells (MNO). Many values of O2 consumption predicted from the diffusion model exceeded $M_{mt} + M_{NO}$. In contrast, reported values of O2 consumption for endothelial and smooth muscle cell suspensions and vascular strips in vitro do not exceed $M_{mt}$. We conjecture that most of the reported values of intravascular O2 flux are overestimated, and the likely source is in the experimental estimates of convective O2 transport at upstream and downstream points of unbranched vascular segments.

microcirculation; oxygen diffusion; endothelial cell; smooth muscle cell; arterioles; nitric oxide

O2 diffusion from arterioles was demonstrated by Dul- ing and Berne (12) and subsequently quantified by a number of researchers in different species and tissues, e.g., brain (13, 27, 73), muscle (38, 39), liver and pancreas (59, 60), and mesentery (71). Analysis of the data by Kuo and Pittman (38, 39) showed that the experimentally observed rate of O2 transfer from the lumen into the wall was an order of magnitude higher than that predicted by a theoretical model (57). These results were corroborated by a more geometrically detailed model (58). To explain this discrepancy, Popel et al. (57) hypothesized a significantly higher (up to two orders of magnitude) in vivo tissue permeability to O2 (Krogh diffusion coefficient), but subsequent specially designed experiments did not confirm this hypothesis, although a significant correction of a factor of two was found (4, 45). Previous theoretical analyses of precapillary transport assumed an O2 consumption rate of the vascular wall (M) similar to that of resting muscle [on the basis of experiments with arterial smooth muscle (34)] or assumed it to be negligible (25, 56, 57, 76). Tsai et al. (71) proposed that the higher-than-expected O2 flux can be explained by high M, two orders of magnitude higher than that of the surrounding tissue in their experiments using the rat mesentery preparation.

In this study, we analyzed existing data from a variety of sources on O2 consumption by endothelial and smooth muscle cells in suspension and by vascular segments in vitro and in vivo. An O2 consumption rate based on the maximum mitochondrial O2 respiration rate (Mmit) was evaluated with the use of available data on mitochondrial content of endothelial and smooth muscle cells. We also examined one of the extramitochondrial pathways by analyzing experimental measurements of nitric oxide (NO) production in the cytosol of the endothelial cell and found that the O2 consumption rate for producing NO, $M_{NO}$, is at least an order of magnitude smaller than the maximum consumption associated with the mitochondrial pathway. We have shown that the O2 consumption in cell suspensions and vascular segments in vitro is below the estimated $M_{mt}$. In contrast, many estimates of O2 consumption from in vivo experiments on the basis of direct measurements of microvascular hemoglobin O2 saturation gradients and blood flow rate in single unbranched vessels exceed $M_{mt}$ by one or two orders of magnitude. In an attempt to resolve this problem, we estimated the sensitivity of the intravascular flux ($J_i$) to changes in $M$ for given intravascular ($P_i$) and perivascular ($P_o$) PO2 values and found that the predicted fluxes were nearly constant at $\sim 10^{-6}$ ml O2 · cm$^{-2}$ · s$^{-1}$ for $M$ spanning over four orders of magnitude. We conjectured that precapillary $J_i$ estimates reported by several laboratories are overestimated by as much as one or two orders of magni-
tude, and we discussed possible measurement artifacts that can account for the overestimates.

RESULTS

In this section, we first present the estimated $M_{mt}$ followed by $M_{NO}$ (Table 1). O₂ consumption for cell suspensions and vascular segments measured in vitro are presented in Tables 2 and 3, respectively. Next, the calculations of O₂ flux at the luminal surface of the arteriolar wall on the basis of in vivo measurements of longitudinal hemoglobin O₂ saturation ($S_{O₂}$) or $P_{O₂}$ gradients and blood flow rates in microvessels of different sizes in several tissues are presented in Table 4. One-layer and a two-layer diffusion models representing the vascular wall are used to evaluate the upper and lower bounds of $M$ and $P_e$. We used these data to calculate physical bounds for O₂ consumption in the vascular wall in Table 5 and showed that in most cases even lower bounds exceed the $M_{mt}$. We repeated the calculations for some of the cases for a two-layer model, in which we estimated the physical bounds of O₂ consumption for the endothelial cell layer and assumed O₂ consumption for the smooth muscle layer on the basis of experimental data. We then performed a sensitivity analysis of intravascular O₂ flux over several orders of magnitude of $M$.

$M_{mt}$: The mitochondrial volume content in capillary endothelial cells ranges between 2 and 5% for a variety of tissues (49). For smooth muscle cells, the mitochondrial volume content is ~5% (61). If we know the maximum mitochondrial respiration rate, we can estimate the $M_{mt}$. In the mitochondria of locomotory muscles of mammals running at their maximum aerobic capacity ($V_{O₂,\text{max}}$), the O₂ consumption rate is $8.3 \times 10^{-2}$ ml O₂ · ml mitochondria $^{-1}$ · s$^{-1}$ (23). Interestingly, the respiration rate of 0.167 ml O₂ · ml$^{-1}$ · s$^{-1}$ for mitochondria in hummingbird flight muscles is approximately twice that of mammals, and these mitochondria also contain twice the amount of oxidative enzymes (65). It is known that the respiration rate of mitochondria at $V_{O₂,\text{max}}$ is ~80% of the maximum rate that can be achieved in suspensions with appropriate substrates (23). Thus the maximum respiration rate is estimated to be 0.1 ml O₂ · ml mitochondria $^{-1}$ · s$^{-1}$. Therefore, assuming a mitochondrial volume content of vascular wall of 5% as a maximum, the $M_{mt}$ for vascular wall can be estimated to be $5 \times 10^{-3}$ ml O₂ · ml$^{-1}$ · s$^{-1}$.

This estimate does not take into account O₂ consumption outside the mitochondria. Jobsis (29) stated that extramitochondrial consumption (sometimes referred to as cyanide-insensitive consumption) could account for 10–15% of the total consumption. In the following section, we show that $M_{NO}$ is at least an order of magnitude smaller than $M_{mt}$.

**Consumption of O₂ by EC for the production of NO.** The intense interest and rapid progress in the study of NO synthesis in biological tissues has developed primarily because 1) NO synthesis has been found in a variety of cell types, 2) NO regulates and affects physiological processes, and 3) NO synthesis via the oxidation of L-arginine has been shown to involve unusual oxidative chemistry. The primary pathway for the production of NO is from L-arginine that is catalyzed by the enzyme NO synthase (NOS) (64). NOS is found in the cytosol of the endothelial cell and can hence represent a possible site for O₂ consumption outside the mitochondria. In Table 1, we have presented values of $M_{NO}$ measured under different conditions. All values shown have been calculated from the amount of NO produced, with the use of the stoichiometric ratio of two molecules of O₂ consumed for every molecule of NO produced (64). Clementi et al. (7) have studied in detail the mechanism by which endothelial cells regulate their O₂ consumption. Their experiments showed that NO generated by vascular endothelial cells under basal and stimulated conditions modulates the O₂ concentration near the cells. This action occurs at the cytochrome c oxidase in the mitochondria and depends on the influx of Ca²⁺. Thus NO plays a physiological role in adjusting the capacity of this enzyme to use O₂, allowing endothelial cells to adapt to acute changes in their environment. In a cell suspension having a density of $10^7$ cells/ml, the initial rate that was also the peak $M_{NO}$ was estimated to be $2.8 \times 10^{-4}$ ml O₂ · ml cell$^{-1}$ · s$^{-1}$. We converted the values from per cell basis to per cell volume basis using the microvascular endothelial cell volume of 400 μm³ reported by Haas and Duling (20). Endothelial cell dimensions in large vessels presented by Levesque and Nerem (41) are consistent with those reported in Haas and Duling (20). For the remainder of the experiment, cell respiration was inhibited in parallel with the generation of NO. These results suggest that, whereas $M_{NO}$ can be as high as $~10^{-4}$ ml O₂ · ml$^{-1}$ · s$^{-1}$, NO itself is responsible for inhibiting the predominant pathways for O₂ consumption in the mitochondria, thus possibly reducing the overall $M$.

The maximum value of $M_{NO}$ ($~10^{-4}$ ml O₂ · ml$^{-1}$ · s$^{-1}$) is measured for bradykinin and shear stress-stimulated NO production as estimated from experiments (7, 19) and a mathematical model (72). The lowest values of $M_{NO}$ are those in which NO was not stimulated by an agonist and are $~10^{-6}$ ml O₂ · ml$^{-1}$ · s$^{-1}$ (2, 36, 40). NO production data reported as per milligram

<table>
<thead>
<tr>
<th>$M_{NO}$, ml O₂ · ml$^{-1}$ · s$^{-1}$</th>
<th>Conditions Under Which NO Was Produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.55 × 10$^{-6}$</td>
<td>Basal rate (2)</td>
</tr>
<tr>
<td>2.81 × 10$^{-4}$</td>
<td>Bradykinin stimulated (7)</td>
</tr>
<tr>
<td>4.76 × 10$^{-4}$</td>
<td>Shear stress stimulated (36)</td>
</tr>
<tr>
<td>7.8 × 10$^{-4}$</td>
<td>Shear stress and bradykinin stimulated (19)</td>
</tr>
<tr>
<td>1.87 × 10$^{-5}$</td>
<td>Vascular endothelial growth factor stimulated (22)</td>
</tr>
<tr>
<td>7.62 × 10$^{-7}$</td>
<td>Estimated from model for activated NO synthase (40)</td>
</tr>
<tr>
<td>6.09 × 10$^{-4}$</td>
<td>Estimated from model for bradykinin NO synthase (72)</td>
</tr>
</tbody>
</table>

$M$, O₂ consumption; NO, nitric oxide. Numbers in parentheses indicate references.
of protein (2, 19, 36) have been converted on a per milliliter basis by using the measured protein content in endothelial cells of 0.1 mg protein/10⁶ cells (2). Therefore, MNO is at least an order of magnitude lower than Mmt. In principle, it is possible that O₂ utilization in arteriolar endothelial cells in vivo, through some other pathway, is significantly higher than is presently believed, but to the best of our knowledge, no such pathway has been identified.

**O₂ consumption by endothelial and smooth muscle cells.** Table 2 summarizes measurements of O₂ consumption rates for endothelial cells (Mₑ) and smooth muscle cell suspensions (Mₛ). The original sources present the consumption rates on a per cell basis. We converted these to a cell volume basis using the cell volume for microvascular endothelial cells and smooth muscle cells as estimated in Haas and Duling (20): 400 μm³ for endothelial cells and 3,000 μm³ for smooth muscle cells.

O₂ consumption measurements made by Kjellstrom et al. (32) in cell cultures indicate a dependence on the source of the cell. Endothelial cell cultures from a bovine aortic cell line exhibit a respiration rate that is several times smaller than cultures derived from the rat pulmonary artery when grown in the same cell nutrient media. Data presented by Motterlini et al. (47) for O₂ consumption on a cell count basis (per million cells) appear to indicate that smooth muscle cells consume more O₂ than endothelial cells. However, this is not the case when the same data are presented in terms of cell volume, because the volume of a smooth muscle cell is ~10 times larger than that of an endothelial cell. Note that MNO values presented in Table 1 are of the same order of magnitude or lower compared with Mₑ in suspension presented in Table 2. Bruttig and Joyner (5) reported Mₑ and Mₛ that were four to five orders of magnitude higher than the values presented in Table 2; values reported by Kuehl et al. (37) are two or three orders of magnitude higher. The source of this discrepancy is unknown.

Table 3 lists M for vascular segments presented on the basis of wet tissue volume. In most cases, data have been reported in terms of dry weight and we have converted them to wet tissue volume by first dividing the former by the reported percentage value of dry weight with respect to wet weight (20–27%) and then by multiplying it with the tissue density of 1.06 g/ml. M in vascular segments shown in Table 3 (9, 30, 33–35, 46, 48, 51, 52) is generally lower than that in cell suspensions (17, 32, 47, 63). In most cases, the vascular segments were devoid of the adventitial layer and consisted of only the intima-media region of the vessel wall, essentially containing endothelial and smooth muscle cells. Importantly, in both groups M is below the value of 5 × 10⁻³ ml O₂ · ml⁻¹ · s⁻¹, corresponding to Mmt. In Figure 1, we compiled all of the experimental values of M in the vascular wall listed in Tables 2 and 3. Mmt is presented as a horizontal line.

The respiration rates for smooth muscle cell suspensions varied depending on the substrate in the nutrient media (17). The difference may be due to substrate participation at different points along the tricarboxylic acid cycle. This has also been observed for vascular

### Table 2. Experimental measurements of M by endothelial and smooth muscle cell suspensions

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>M, ml O₂ ml⁻¹ · s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td></td>
</tr>
<tr>
<td>Bovine aorta (32)</td>
<td>2.8 × 10⁻⁴</td>
</tr>
<tr>
<td>Rat pulmonary artery (32)</td>
<td>1.5 × 10⁻³</td>
</tr>
<tr>
<td>Human umbilical vein (32)</td>
<td>1.4 × 10⁻³</td>
</tr>
<tr>
<td>Porcine aorta (47)</td>
<td>1.0 × 10⁻³</td>
</tr>
<tr>
<td>Porcine aorta (28)</td>
<td>1.4 × 10⁻⁴</td>
</tr>
<tr>
<td>Human umbilical vein (63)</td>
<td>2.5 × 10⁻³</td>
</tr>
<tr>
<td>SMC</td>
<td></td>
</tr>
<tr>
<td>Porcine aorta (47)</td>
<td>3.7 × 10⁻⁴</td>
</tr>
<tr>
<td>Rat aorta (17)</td>
<td></td>
</tr>
<tr>
<td>Substrate</td>
<td></td>
</tr>
<tr>
<td>Pyruvate</td>
<td>4.5 × 10⁻⁴</td>
</tr>
<tr>
<td>Succinate</td>
<td>8.3 × 10⁻⁴</td>
</tr>
<tr>
<td>TMPD-ascorbate</td>
<td>8.1 × 10⁻⁴</td>
</tr>
</tbody>
</table>

M is measured on a cell volume basis; EC, endothelial cells; SMC, smooth muscle cells. Numbers in parentheses indicate references.

### Table 3. Experimental measurements of M in vascular segments in vitro

<table>
<thead>
<tr>
<th>Vessel Type</th>
<th>M, ml O₂ ml⁻¹ · s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit carotid artery* (33)</td>
<td></td>
</tr>
<tr>
<td>Tyrode substrate with 0.004 M succinate</td>
<td></td>
</tr>
<tr>
<td>Adventititia</td>
<td>2.3 × 10⁻⁴</td>
</tr>
<tr>
<td>Intima-media</td>
<td>3.5 × 10⁻⁴</td>
</tr>
<tr>
<td>Intact vessel</td>
<td>1.3 × 10⁻⁴</td>
</tr>
<tr>
<td>No exogenous substrate</td>
<td></td>
</tr>
<tr>
<td>Adventititia</td>
<td>2.7 × 10⁻⁵</td>
</tr>
<tr>
<td>Intima-media</td>
<td>3.8 × 10⁻⁵</td>
</tr>
<tr>
<td>Intact vessel</td>
<td>7.5 × 10⁻⁵</td>
</tr>
<tr>
<td>Tyrode substrate with 0.0001 M 2,4-dinitrophenol</td>
<td></td>
</tr>
<tr>
<td>Adventititia</td>
<td>1.6 × 10⁻⁵</td>
</tr>
<tr>
<td>Intima-media</td>
<td>2.8 × 10⁻⁵</td>
</tr>
<tr>
<td>Intact vessel</td>
<td>6.9 × 10⁻⁵</td>
</tr>
<tr>
<td>Rabbit aorta (46)</td>
<td></td>
</tr>
<tr>
<td>Intima with destroyed EC</td>
<td>3.8 × 10⁻⁴</td>
</tr>
<tr>
<td>Intima with intact EC</td>
<td>5.7 × 10⁻⁵</td>
</tr>
<tr>
<td>Dog femoral artery (34)</td>
<td>1.7 × 10⁻⁴</td>
</tr>
<tr>
<td>Cat pial artery (48)</td>
<td>1.2 × 10⁻⁴</td>
</tr>
<tr>
<td>Human umbilical artery (9)</td>
<td>2.1 × 10⁻⁴</td>
</tr>
<tr>
<td>Rabbit aorta (30)</td>
<td>7.5 × 10⁻⁵</td>
</tr>
<tr>
<td>Bovine cerebral microvessels (66)</td>
<td></td>
</tr>
<tr>
<td>Control With succinate</td>
<td>5.5 × 10⁻⁴</td>
</tr>
<tr>
<td>Porcine coronary artery (51)</td>
<td>1.6 × 10⁻⁴</td>
</tr>
<tr>
<td>Vasocostriction</td>
<td>7.2 × 10⁻⁵</td>
</tr>
<tr>
<td>Porcine carotid artery (3)</td>
<td>5.3 × 10⁻⁵</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Vasocostriction</td>
<td>5.6 × 10⁻⁴</td>
</tr>
<tr>
<td>Bovine mesenteric vein (52)</td>
<td>5.3 × 10⁻⁵</td>
</tr>
<tr>
<td>Rabbit femoral artery (10)</td>
<td>9.9 × 10⁻⁵</td>
</tr>
<tr>
<td>Porcine carotid artery (55)</td>
<td>1.9 × 10⁻⁴</td>
</tr>
<tr>
<td>Porcine carotid artery (35)</td>
<td>3.3 × 10⁻⁵</td>
</tr>
<tr>
<td>Porcine carotid artery (50)</td>
<td>1.3 × 10⁻⁴</td>
</tr>
<tr>
<td>Human arteriole (24)</td>
<td></td>
</tr>
<tr>
<td>With anesthesia</td>
<td>1.0 × 10⁻⁴</td>
</tr>
<tr>
<td>Without anesthesia</td>
<td>2.4 × 10⁻⁴</td>
</tr>
<tr>
<td>Rabbit abdominal aorta in vivo (6)</td>
<td>1.3 × 10⁻⁴</td>
</tr>
<tr>
<td>Rabbit thoracic aorta in vivo (6)</td>
<td>9.8 × 10⁻⁵</td>
</tr>
<tr>
<td>Dog thoracic aorta in vivo (6)</td>
<td>1.5 × 10⁻⁴</td>
</tr>
</tbody>
</table>
segments in which the respiration rates of each layer exhibited a change when the substrate in the nutrient media changed (33).

In the above studies, M was measured directly by placing the vascular segments in a sealed chamber with oxygenated solution. In two studies, PO2 was measured with O2 electrodes at several depths in the vascular wall in vivo (6) or in vitro (10, 55) and M was calculated using a model of O2 diffusion.

Experimental studies show an increase in M with vascular stimulation and contraction. These values may vary from approximately twice the resting muscle M (35, 51) to as much as 10 times (3). Values of M reported in Table 3 with the use of the data from Paul (50) have been calculated by estimating the isometric wall stress in a vessel having a blood pressure of 90 mmHg by multiplying the vessel radius by the arterial blood pressure and dividing the result with the corresponding vessel thickness (the Law of Laplace). Studies conducted by Paul (50) indicate a linear trend in ATP consumption with increasing isometric stress in the vessel wall. The corresponding ATP consumption was computed with the use of the relationship between ATP consumption and isometric force (50). On the basis of the respiration cycle, the O2 consumed was calculated from the ATP consumed by dividing the latter by the stoichiometric ratio 6.42 moles of ATP per mole of O2.

Note that the values of vascular tissue consumption may vary from approximately twice the resting muscle M (35, 51) to as much as 10 times (3). Values of M reported in Table 3 with the use of the data from Paul (50) have been calculated by estimating the isometric wall stress in a vessel having a blood pressure of 90 mmHg by multiplying the vessel radius by the arterial blood pressure and dividing the result with the corresponding vessel thickness (the Law of Laplace). Studies conducted by Paul (50) indicate a linear trend in ATP consumption with increasing isometric stress in the vessel wall. The corresponding ATP consumption was computed with the use of the relationship between ATP consumption and isometric force (50). On the basis of the respiration cycle, the O2 consumed was calculated from the ATP consumed by dividing the latter by the stoichiometric ratio 6.42 moles of ATP per mole of O2.

To calculate Ji from in vivo measurements in microvessels, we showed that, with noted exceptions, in vitro measurements in cell suspensions and in vivo measurements in arteries and vascular segments yield values of M smaller than Mmt. We then analyzed in vivo data from different laboratories in different species and tissues from unbranched microvascular segments, on the basis of measurements of longitudinal hemoglobin SO2 or PO2 gradients. We have shown that in most cases either the data cannot be interpreted in terms of a diffusion model or the predicted values of M exceed Mmt or even Mmt + MNO.

For a cylindrical segment of blood vessel with a luminal diameter d and length Δz, the diffusive loss of O2 can be estimated as

\[ Q[Hb]C_b \Delta S = \pi d \Delta z J_i \]  

where \( Q = (\pi d^2/4)v \) is the volumetric blood flow rate, \( v \) is the mean velocity, [Hb] is the concentration of hemoglobin in the blood, \( C_b \) is the O2 binding capacity of the hemoglobin, \( \Delta S \) is the saturation difference between the upstream and downstream points along the vessel segment, and \( J_i \) is given per unit area at the vessel wall (luminal surface) averaged over the vessel circumference (53). \( J_i \) can be calculated from Eq. 1 with all other parameters determined experimentally. In Table 4, we showed the microvascular parameters \( d, v, \Delta S/\Delta z \), and [Hb] for eight different sets of in vivo measurements necessary for calculating \( J_i \). [Hb] for hamster and rat was calculated as the product of the discharge hematocrit and [Hb] in a single red blood cell (RBC) whose value is taken to be 19.58 mM (67). It was not necessary to calculate the \( J_i \) for the data of Seiyama et al. (59, 60) since the authors had already carried out these calculations. Pi values were available for Tsai et al. (71) and Torres Filho et al. (70) since...
these authors used the phosphorescence quenching method to measure \( P_i \); in these studies, the authors determined \( \Delta S \) values by converting \( \Delta P_{O_2} \) into \( \Delta S \) values with the Hill equation. For all of the other sources in which \( S_{O_2} \) was determined microspectrophotometrically, \( S_{O_2} \) values were converted into \( P_{O_2} \) with the use of the Hill equation. The Hill equation parameters \( n \) (cooperativity of Hb) and \( P_{50} \) (O2 tension corresponding to 50% saturation) for rat were taken from Altman and Dittmer (1) and those of the hamster retractor muscle from Ellsworth et al. (16). \( K \) for the vascular wall was estimated to be \( 3.17 \times 10^{-10} \) ml \( O_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1} \) and was calculated as the product of the diffusivity (\( D \)) in human arteries measured to be \( 0.96 \times 10^{-5} \) cm\(^2\)/s (31), and the solubility coefficient (\( \alpha \)) reported for many tissues to be \( 3.3 \times 10^{-5} \) ml \( O_2 \cdot \text{cm}^{-3} \cdot \text{Torr}^{-1} \) (14). \( D \) is lower by a factor of \( \sim 2.5 \) when compared with that of the hamster retractor muscle at 37°C (2.42 \( \times \) 10\(^{-5} \) cm\(^2\)/s) (4, 14). For endothelial cells in vitro, \( D \) has been found to vary between 0.14–0.87 \( \times \) 10\(^{-5} \) cm\(^2\)/s (43).

### Physiological ranges for \( P_o \) and \( M \) using a one-layer diffusion model.
In a diffusion model of the vascular wall, the values of \( J_o \), \( P_i \), \( P_o \), and \( M \) are not independent; if \( J_o \) and \( P_o \) are known from experiments, a range of possible values for \( P_o \) and \( M \) can be obtained subject to physical conditions \( P_o \geq 0 \), \( M \geq 0 \); if \( J_o \), \( P_i \), and \( P_o \) are known, then \( M \) can be uniquely determined. Therefore, to estimate the bounds of \( P_o \) and \( M \) for given values of other parameters, including \( P_i \) and \( J_o \), we solved the problem of \( O_2 \) transport in the vascular wall. The vessel wall was modeled by an axially symmetrical diffusion equation

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P}{\partial r} \right) - \frac{M}{K} = 0
\]

where \( r \) is the radius.

The boundary conditions are applied at the inside and outside surfaces of the vessel wall

\[
r = r_o, \quad P = P_o; \quad r = r_i, \quad P = P_i
\]

where \( r_i \) is the interior and \( r_o \) is the exterior radius of the vessel.

Integrating Eq. 2 and applying boundary conditions Eq. 3, we get

\[
P = P_i + \frac{M(r_i^2 - r_o^2)}{4K} + \frac{P_i - P_o + \frac{M(r_o^2 - r_i^2)}{4K}}{\ln(r_i/r_o)} \ln(r/r_o)
\]
With Eq. 4 we obtain an expression for \( J_1 \)

\[
J_1 = -k_0 \rho / r |_{r=r_i} = \frac{K(P_i - P_o)}{r_i \ln(r_o/r_i)} - M \left[ \frac{r_i}{2} + \frac{(r_o^2 - r_i^2)}{4r_i \ln(r_o/r_i)} \right]
\]

and the perivascular flux (\( J_o \))

\[
J_o = -k_0 \rho / r |_{r=r_o} = \frac{K(P_i - P_o)}{r_o \ln(r_o/r_i)} - M \left[ \frac{r_o}{2} + \frac{(r_o^2 - r_i^2)}{4r_o \ln(r_o/r_i)} \right]
\]

M can be expressed from mass balance using \( J_1 \) and \( J_o \)

\[
M = \pi(r_o^2 - r_i^2) = 2\pi r_i J_1 - 2\pi r_o J_o
\]

Rearranging Eq. 7, we obtain \( J_o \) in terms of \( J_1 \) and M

\[
J_o = \frac{r_i}{r_o} J_1 - M \left[ \frac{r_o^2 - r_i^2}{2r_o} \right]
\]

If we require that the vessel wall be supplied with O\(_2\) from the lumen and not from the parenchymal side, then \( J_o \geq 0 \) in Eq. 8, and we obtain the upper bound on the M, \( M_{max} \), when \( J_o = 0 \) (i.e., all of the O\(_2\) diffusing from the lumen is consumed by the vascular wall)

\[
M_{max} = \frac{2r_o J_1}{(r_o^2 - r_i^2)}
\]

Eliminating \( J_o \) from Eqs. 6 and 8 gives us \( P_o \) in terms of \( P_i \) and \( J_1 \)

\[
P_o = P_i - \frac{r_i \ln(r_o/r_i)}{K} J_1 + \frac{M}{2K} \left[ \frac{(r_o^2 - r_i^2)}{2} - r_i^2 \ln(r_o/r_i) \right]
\]

The term in square brackets can be shown to be >0. Since \( P_o \geq 0 \), Eq. 10 yields

\[
\left[ r_i \ln(r_o/r_i) J_1 - K P_i \right] \leq \frac{M}{2} \left[ \frac{(r_o^2 - r_i^2)}{2} - r_i^2 \ln(r_o/r_i) \right]
\]

This inequality can be satisfied in two ways. Case 1 is

\[
P_i > \frac{r_i \ln(r_o/r_i)}{K} J_1
\]

then

\[
0 \leq M \leq M_{max} \quad \text{and} \quad P_{o min} \leq P \leq P_{o max}
\]

where \( M_{max} \) is given by Eq. 9, \( P_{o min} \) is the minimum possible \( P_o \), and \( P_{o max} \) is the maximum \( P_o \). \( P_{o min} \) is obtained from Eq. 10 by setting \( M = 0 \) and is given by

\[
P_{o min} = P_i - \left[ \frac{J_1 \ln(r_o/r_i)}{K} \right]
\]

and the \( P_{o max} \) is obtained by substituting Eq. 9 into Eq. 10

\[
P_{o max} = P_i - \left[ \frac{J_1}{K} \left( \frac{r_o^2}{r_o^2 - r_i^2} \ln(r_o/r_i) - 0.5 \right) \right]
\]

The schematic representing case 1 is shown in Fig. 2A. This case is physiologically possible since both \( P_{o min} \) and \( P_{o max} \) are positive. It is important to note that the \( P_o \) increases as \( M \) increases. This appears to be counterintuitive when compared with the conventional thinking in which higher \( M \) results in a higher \( J_1 \) and a correspondingly lower \( P_o \). Conventionally, e.g., under conditions of the Krogh tissue cylinder model, \( J_1 \) is proportional to tissue O\(_2\) consumption (\( M_t \)); thus an increase in \( M_t \) leads to an increase in \( J_1 \) (i.e., an
increase in the negative slope of the $P_o$ profile at the luminal surface) and thus a decrease in $P_o$. In contrast, in the case under consideration, $J_i$ is fixed when $M$ varies and the above argument is not applicable. Similar behavior will also be seen in the next two cases. case 2 is

$$P_i \leq \frac{r_i \ln(r_o/r_i)}{K} J_i$$

(14a)

case 2a then

$$M_{\text{min}} < M \leq M_{\text{max}} \quad \text{and} \quad 0 < P \leq P_{o \text{ max}}$$

(14b)

and, where $M_{\text{min}}$ is obtained from Eq. 10 for $P_o = 0$

$$M_{\text{min}} = \frac{2[r_i \ln(r_o/r_i)J_i - K P_i]}{r_o^2 - r_i^2 - r_i^2 \ln(r_o/r_i)}$$

(15)

A schematic of case 2a is presented in Fig. 2B. The $P_o$ for $M = 0$ is negative, which is not possible. Hence, a physiologically possible case would have to be $P_o > 0$, $M > M_{\text{min}}$. The lower bound on the $P_i$ is a strict inequality, since it is not possible to have $P_o = 0$ for a finite flux leaving the wall.

If the model parameters are such that Eqs. 9–10 yield $P_{o \text{ max}} < 0$, then there is no solution to the problem, i.e., there are no physical values of $M$ and $P_o$ that satisfy the above relationships; thus case 2b has no solution if $P_{o \text{ max}} < 0$, which is represented in Fig. 2C. Note the increasing slope with respect to the horizontal axis of the $P_o$ profile at $r = r_i$ as one moves from case 1 to 2a to 2b in Fig. 2. This suggests that an in vivo measurement with a very high flux is most likely to fall under case 2.

All three cases are represented in the data analysis in Table 5, in which the entries represented by blanks are those of case 2b. The values for the wall thickness, $w$, necessary for these calculations were chosen as follows. Swain and Pittman (67) optically measured $w$ and $d$ for different order arterioles in the hamster retractor muscle and found the following correlation: $w = 0.24d + 0.39 \mu m$. We use this relationship to estimate $w$ for all blood vessels with diameters $> 25 \mu m$ in Table 4. On the basis of measurements from Haas and Duling (20), a $w$ of 6.5 $\mu m$ (6 $\mu m$ for a single layer of smooth muscle cells and 0.5 $\mu m$ for a layer of endothelial cells) was used for our calculations in Table 5 for all arterioles with $d < 25 \mu m$. The capillary wall was assumed to consist of a layer of endothelial cells with a thickness of 0.5 $\mu m$.

Clearly, there is a problem in interpreting many of the experiments listed in Table 5 (13 out of 32) since

<table>
<thead>
<tr>
<th>Type of Vessel</th>
<th>$J_i$, ml O$_2$ cm$^{-2}$ s$^{-1}$</th>
<th>$P_o$ Torr</th>
<th>Case</th>
<th>$P_{o \text{ min}},$ Torr</th>
<th>$P_{o \text{ max}},$ Torr</th>
<th>$M_{o \text{ min}},$ ml O$_2$ ml$^{-1}$ s$^{-1}$</th>
<th>$M_{o \text{ max}},$ ml O$_2$ ml$^{-1}$ s$^{-1}$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary</td>
<td>$8.0 \times 10^{-7}$</td>
<td>30.0</td>
<td>1</td>
<td>29.99</td>
<td>30.02</td>
<td>0</td>
<td>0.030</td>
<td>Hamster retractor muscle (16)</td>
</tr>
<tr>
<td>Capillary</td>
<td>$1.2 \times 10^{-6}$</td>
<td>33.1</td>
<td>1</td>
<td>33.01</td>
<td>33.05</td>
<td>0</td>
<td>0.047</td>
<td>Hamster retractor muscle (62)</td>
</tr>
<tr>
<td>Arteriole</td>
<td>$6.3 \times 10^{-6}$</td>
<td>35.0</td>
<td>2a</td>
<td>6.5</td>
<td>0.094</td>
<td>0.141</td>
<td>0.091</td>
<td>Rat retractor muscle (60)</td>
</tr>
<tr>
<td>Group 1</td>
<td>$1.7 \times 10^{-6}$</td>
<td>19.6</td>
<td>1</td>
<td>6.0</td>
<td>11.6</td>
<td>0.040</td>
<td>0.074</td>
<td>Rat liver (59)</td>
</tr>
<tr>
<td>Group 2</td>
<td>$3.2 \times 10^{-6}$</td>
<td>21.0</td>
<td>2a</td>
<td>6.3</td>
<td>0.029</td>
<td>0.074</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>$2.0 \times 10^{-6}$</td>
<td>19.2</td>
<td>1</td>
<td>3.8</td>
<td>10.1</td>
<td>0</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>$1.1 \times 10^{-5}$</td>
<td>17.9</td>
<td>1</td>
<td>9.4</td>
<td>12.9</td>
<td>0</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>1A normal</td>
<td>$5.1 \times 10^{-6}$</td>
<td>35.6</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>2A normal</td>
<td>$5.0 \times 10^{-6}$</td>
<td>31.8</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>3A normal</td>
<td>$5.8 \times 10^{-6}$</td>
<td>31.3</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>4A normal</td>
<td>$4.2 \times 10^{-6}$</td>
<td>27.6</td>
<td>2a</td>
<td>7.3</td>
<td>0.06</td>
<td>0.111</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>1A dilated</td>
<td>$2.8 \times 10^{-6}$</td>
<td>44.1</td>
<td>2a</td>
<td>16.5</td>
<td>0.01</td>
<td>0.096</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>2A diluted</td>
<td>$3.1 \times 10^{-6}$</td>
<td>43.0</td>
<td>2a</td>
<td>18.0</td>
<td>0.01</td>
<td>0.096</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>3A diluted</td>
<td>$4.7 \times 10^{-6}$</td>
<td>39.4</td>
<td>2a</td>
<td>8.7</td>
<td>0.065</td>
<td>0.096</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>4A diluted</td>
<td>$2.5 \times 10^{-6}$</td>
<td>37.8</td>
<td>1</td>
<td>16.4</td>
<td>26.4</td>
<td>0</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>1A normal</td>
<td>$4.9 \times 10^{-6}$</td>
<td>38.6</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>2A normal</td>
<td>$8.2 \times 10^{-6}$</td>
<td>37.1</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>3A normal</td>
<td>$8.4 \times 10^{-6}$</td>
<td>31.8</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>4A normal</td>
<td>$6.5 \times 10^{-6}$</td>
<td>29.1</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>1A conc</td>
<td>$1.5 \times 10^{-4}$</td>
<td>38.6</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>2A conc</td>
<td>$1.1 \times 10^{-4}$</td>
<td>37.1</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>3A conc</td>
<td>$1.1 \times 10^{-4}$</td>
<td>31.8</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>4A conc</td>
<td>$6.0 \times 10^{-6}$</td>
<td>29.1</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>$4.0 \times 10^{-6}$</td>
<td>37.1</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>$4.2 \times 10^{-6}$</td>
<td>35.6</td>
<td>2a</td>
<td>0.8</td>
<td>0.06</td>
<td>0.066</td>
<td>0.066</td>
<td></td>
</tr>
<tr>
<td>3A</td>
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<td>30.7</td>
<td>2b</td>
<td></td>
<td></td>
<td>0.06</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td>$4.8 \times 10^{-6}$</td>
<td>25.6</td>
<td>2a</td>
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<td>0.106</td>
<td>0.128</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>Arteriole</td>
<td>$2.7 \times 10^{-6}$</td>
<td>43.0</td>
<td>1</td>
<td>18.5</td>
<td>29.9</td>
<td>0</td>
<td>0.074</td>
<td>Rat mesentery (71)</td>
</tr>
<tr>
<td>1A</td>
<td>$4.1 \times 10^{-6}$</td>
<td>51.8</td>
<td>2a</td>
<td>2.1</td>
<td>0.044</td>
<td>0.047</td>
<td>0.047</td>
<td>Hamster skinfold (70)</td>
</tr>
<tr>
<td>2A</td>
<td>$2.1 \times 10^{-6}$</td>
<td>44.1</td>
<td>1</td>
<td>20.0</td>
<td>31.2</td>
<td>0</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>$6.7 \times 10^{-6}$</td>
<td>39.9</td>
<td>1</td>
<td>34.3</td>
<td>36.7</td>
<td>0</td>
<td>0.017</td>
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</tr>
<tr>
<td>4A</td>
<td>$1.5 \times 10^{-6}$</td>
<td>34.0</td>
<td>1</td>
<td>32.8</td>
<td>33.3</td>
<td>0</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

Data are based on a 1-layer model and in vivo $J_i$ calculated in Table 4. $P_o$, intravascular O$_2$ tension; $P_{o \text{ min}}$, minimum O$_2$; $P_{o \text{ max}}$, maximum O$_2$; $M_{o \text{ min}}$, minimum wall consumption rate; $M_{o \text{ max}}$, maximum wall consumption rate.
they fall under case 2b in which no physical values of $P_o$ and $M$ can be found. In 9 out of 19 cases for arterioles shown in Table 5 (capillaries excluded), the minimum $M$ ($M_{\text{min}}$) exceeds $M_{\text{mt}}$, and in 8 out of 17 cases $M_{\text{min}}$ also exceeds $M_{\text{mt}} + M_{\text{NO}} (5.8 \times 10^{-3} \text{ ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1})$.

Physiological ranges for $P_o$ and $M$ with the use of a two-layer diffusion model. In the one-layer model calculations, we lumped the endothelium and smooth muscle cells together, thus neglecting a possible difference in $O_2$ consumption between these cell types. By considering a two-layer model (derivation presented in Appendix), we show that taking these differences into account does not resolve the problem of interpreting the in vivo data. We chose $M_s$ on the basis of published experimental values. The goal of the calculations was to estimate the physiological limits of the $M_e$ and the $P_o$ on the basis of the in vivo measurements presented in Table 4. In Table 6, we present calculations for three arteriolar cases from Table 4. The $M_s$ is taken to be $10^{-4} \text{ ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ on the basis of measurements presented in Table 2. The $K$ for the endothelial cell layer was taken to be $4.45 \times 10^{-10} \text{ ml O}_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1}$ (43), whereas that of the smooth muscle cell layer was $4.5 \times 10^{-10} \text{ ml O}_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1}$ (1). Values of inner diameter, thickness, $P_i$, and $J_i$ were taken from Table 4. The values of $M_e$ are much higher than the corresponding computed values of $M$ in Table 5 and higher than $M_{\text{mt}}$. This is primarily because we have fixed the $M_s$ that occupy most of the vascular wall to a value that is two orders of magnitude lower than the values of $M$ in Table 5. As a result, $M_e$ that occupies a smaller volume fraction of the vascular wall is in general two orders of magnitude higher than the values of $M$ in Table 5. Increasing the value of $M_s$ from $10^{-4}$ to $10^{-3} \text{ ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ has little effect on the results in Table 6. Because of the thin endothelial cell layer, we also do not encounter case 2b in Table 5 where $P_o > 0$.

Sensitivity of $P_o$ and $M$ to input parameters with the use of the one-layer model. To see the effect of input parameters on the overall results, we varied $K$, the $P_i$, and the thickness of the vascular wall and presented the results in Table 7. Doubling $K$ to $6.34 \times 10^{-10} \text{ ml O}_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1}$ results in a larger number of in vivo measurements falling under case 1 (twice as many). Since doubling the value of $K$ has the greatest effect on the in vivo results, we presented the physiological bounds for some of the in vivo measurements in Table 8. The initial value $K = 3.17 \times 10^{-10} \text{ ml O}_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1}$ is close to the value $3.64 \times 10^{-10} \text{ ml O}_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1}$ taken by Tsai et al. (71), but the calculated transvascular $P_o$ difference of 11.4 Torr in Table 5 is less than the experimentally observed value of 18.1 Torr. Increasing $K$ only further decreased the transvascular $P_o$ difference.

The present calculations assume that $P_i$ is the same as in the vessel on average, corresponding to the measured $S_{O_2}$, whereas in reality there exists a gradient in $P_i$. At present, radial $P_i$ gradients can be determined theoretically using mass transfer coefficients estimated for arteriolar-sized vessels by Hellums et al. (21). The mass transfer coefficient is used to represent the ratio of the $J_i$ and the corresponding driving force in $O_2$ tension. The dimensionless mass transfer coefficient, called the Nusselt number, is defined as

$$\text{Nu} = \frac{2J_i r_i}{K_{pl}(P^* - P_i)} \quad (16)$$

where $K_{pl}$ is the Krogh coefficient for $O_2$ in plasma, $P^*$ is the $O_2$ tension in equilibrium with the mixed mean hemoglobin saturation, $P_i$, and $J_i$ are measured at the vessel wall, and $r_i$ is the internal radius of the vessel. On the basis of the calculations of Hellums et al. (21), for an arteriole with a diameter of 23 $\mu$m and flux of $6 \times 10^{-5} \text{ ml O}_2 \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$, the radial $P_i$ drop, $P^* - P_i$, would be 66 Torr. Performing similar calculations with flux values from Table 4 for corresponding diameters yielded similar values. Obviously, these $P_o$ drops are unrealistically high since they are greater than the measured $P_i$ values in Table 5. On the other hand, if we use an order of magnitude lower flux value, consistent with those calculated from transvascular $P_o$ measurements presented in Fig. 3 and described in Sensitivity of $J_i$ to wall consumption rates, we obtain $P^* - P_i$ of $\approx 5$–6 Torr. Hence, we chose a drop of 5 Torr in the $P_i$ for our sensitivity analysis calculations. When the $P_i$ is decreased by 5 Torr, the number of measurements falling under case 1 and case 2a reduced by one and two, respectively, whereas those of case 2b increased correspondingly by three.

Changes in wall thickness only slightly affected the number of in vivo measurements falling under case 1, and $M_{\text{max}}$ maximum endothelial cell layer consumption rate corresponding to perivascular flux of 0.

### Table 6. Physiological ranges of $P_o$ and $M$ for selected cases in Table 5 on the basis of a two-layer model

<table>
<thead>
<tr>
<th>Type of Vessel</th>
<th>$J_o$, ml O$_2$ cm$^{-2}$ s$^{-1}$</th>
<th>$P_o$, Torr</th>
<th>$P_{\text{min}}$, Torr</th>
<th>$P_{\text{max}}$, Torr</th>
<th>$M_{\text{min}}$, ml O$_2$ ml$^{-1}$ s$^{-1}$</th>
<th>$M_{\text{max}}$, ml O$_2$ ml$^{-1}$ s$^{-1}$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>4A normal</td>
<td>$6.5 \times 10^{-5}$</td>
<td>29.1</td>
<td>0</td>
<td>25.0</td>
<td>0.74</td>
<td>1.15</td>
<td>Hamster retractor muscle (39)</td>
</tr>
<tr>
<td>4A arteriole</td>
<td>$2.7 \times 10^{-5}$</td>
<td>43.0</td>
<td>12.0</td>
<td>41.4</td>
<td>0</td>
<td>0.53</td>
<td>Rat mesentery (71)</td>
</tr>
<tr>
<td>IA</td>
<td>$4.1 \times 10^{-5}$</td>
<td>51.8</td>
<td>32.7</td>
<td>33.8</td>
<td>0</td>
<td>0.026</td>
<td>Hamster skinfold (70)</td>
</tr>
</tbody>
</table>

$M_{\text{min}}$, minimum endothelial cell layer consumption rate; $M_{\text{max}}$, maximum endothelial cell layer consumption rate corresponding to perivascular flux of 0.

### Table 7. Sensitivity of results of the one-layer model with respect to different model parameters

<table>
<thead>
<tr>
<th>No. of Case 1</th>
<th>No. of Case 2a</th>
<th>No. of Case 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of results in Table 5</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Doubling the Krogh coefficient</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Reducing $P_i$ by 5 Torr</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Decreasing wall thickness by 20%</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Increasing wall thickness by 20%</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>
whereas the distribution of cases falling under cases 2a and 2b changed to a larger extent. Hence, the results are most sensitive to a 100% increase in $K$, although no experimental measurements are available in support of such a high vascular wall $K$.

**Sensitivity of $J_i$ to wall consumption rates.** The sensitivity of $J_i$ with respect to $M$ can also be analyzed with the use of Eq. 10 and available experimental data on transvascular $P_o$. With the use of recessed-tip O2 microelectrodes, Duling et al. (13) measured the $P_i$ and $P_o$ for cat pial microvessels with internal diameters ranging from 22 $\mu$m to 230 $\mu$m and found the gradient $(P_i - P_o)/w = 1$ Torr/$\mu$m for vessels of all sizes. Knowing the internal and external vessel diameter and the corresponding $P_o$ for vessels groups in four different vascular orders, we can compute a $J_i$ for $M$ ranging between $10^{-6}$ and $10^{-2}$ ml O$_2$·cm$^{-2}$·s$^{-1}$. The results are presented in Fig. 3. $J_i$ is found to be almost constant for $M$ in the range of $10^{-6}$ to $10^{-4}$ ml O$_2$·cm$^{-1}$·s$^{-1}$, with values of the flux at $\sim (3-4) \times 10^{-6}$ ml O$_2$·cm$^{-2}$·s$^{-1}$. Thereafter, $J_i$ increases by a factor of two when $M$ increases to its respective $M_{max}$ value. The relative sensitivity of $J_i$ to $M$ can be explained using Eq. 5. For small ratios of $w/R_i$, Eq. 5 can be expressed as

$$J_i = K(P_i - P_o)/w + Mw/2 \quad (17)$$

With $K = 3.17 \times 10^{-10}$ ml O$_2$·cm$^{-1}$·Tor$^{-1}$·s$^{-1}$ and $(P_i - P_o)/w = 10^4$ Torr/cm, the first term in Eq. 17 is $3.17 \times 10^{-6}$ ml O$_2$·cm$^{-2}$·s$^{-1}$, for $M = 10^{-4}$ ml O$_2$·cm$^{-2}$·s$^{-1}$ and $w = 2 \times 10^{-3}$ cm, and the second term equals $10^{-7}$ ml O$_2$·cm$^{-2}$·s$^{-1}$. For smaller values of $M$, the contribution of the second term is even smaller.

**DISCUSSION**

We have shown in Table 5 that for 30 reported sets of measurements of arteriolar $J_i$, 13 cases cannot be explained using physically realistic parameters; for the remaining ones, in nine cases $M_{min} > M_{ml}$. We discuss possible reasons for the overestimation of $J_i$.

**Estimates of $J_i$ and $M$ on the basis of in vivo measurements.** The average arteriolar $J_i$ in Table 4 varies between $10^{-6}$ ml O$_2$·cm$^{-2}$·s$^{-1}$ in capillaries and $10^{-4}$ ml O$_2$·cm$^{-2}$·s$^{-1}$ in arterioles; these estimates are based on in vivo measurements of longitudinal hemoglobin O$_2$ saturation gradients ($\Delta S/\Delta z$) or O$_2$ tension ($\Delta P_o/\Delta z$) in unbranched vessel segments. The values of theoretically estimated $M$ in Table 5 range from 0 to 0.16 ml O$_2$·cm$^{-1}$·s$^{-1}$, with a tendency to increase with increasing vascular diameter; this range is shown in Fig. 1 together with in vitro and in vivo data.

In all of the studies, except Ref. 71, the $P_o$ was not measured, and therefore we were only able to estimate possible ranges of $P_o$ and $M$. However, since Tsai et al. (71) measured both $P_i$ and $P_o$ using the phosphoresence decay method, they were able to estimate $M$ at 6.5 ×

**Table 8. Physiological ranges of $P_o$ and $M$**

<table>
<thead>
<tr>
<th>Type of Vessel</th>
<th>$J_i$, ml cm$^{-2}$·s$^{-1}$</th>
<th>$P_o$, Torr</th>
<th>$P_{o_{min}}$, Torr</th>
<th>$P_{o_{max}}$, Torr</th>
<th>$M_{o_{min}}$, ml O$_2$·cm$^{-1}$·s$^{-1}$</th>
<th>$M_{o_{max}}$, ml O$_2$·cm$^{-1}$·s$^{-1}$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>4A normal</td>
<td>$6.5 \times 10^{-5}$</td>
<td>29.1</td>
<td>0</td>
<td>13.2</td>
<td>0.005</td>
<td>0.177</td>
<td>Hamster retractor muscle (39)</td>
</tr>
<tr>
<td>2A arteriole</td>
<td>$2.7 \times 10^{-5}$</td>
<td>43.0</td>
<td>30.9</td>
<td>36.6</td>
<td>0</td>
<td>0.074</td>
<td>Rat mesentery (71)</td>
</tr>
<tr>
<td>1A</td>
<td>$4.1 \times 10^{-5}$</td>
<td>51.8</td>
<td>5.5</td>
<td>26.9</td>
<td>0</td>
<td>0.046</td>
<td>Hamster skinfold (70)</td>
</tr>
</tbody>
</table>

Data are based on a 1-layer model and in vivo $J_i$ calculated in Table 4 with higher Krogh coefficient.

**Fig. 3. Sensitivity of calculated intravascular flux ($J_i$) to vascular wall consumption using experimental measurements of intravascular and perivascular $P_o$ values and 1-layer diffusion model.**
Taking $10^{-2} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, note that this value is an order of magnitude higher than the estimated Mmt ($5 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$). Looking at the overall picture shown in Fig. 1 and Table 5, we hypothesize that there is a problem with most microvascular measurements listed in Table 4. We discuss possible reasons in Possible reasons for the overestimation of intravascular flux.

In another study, Po2 on the surface of rat brain cortex microvessels was measured (73). At normoxia, Po values for arterioles of diameters 7–70 μm fall with decreasing diameter, (Po = 55.7 + 0.45d Torr), and the tissue Po2 (P) measured at a distance of 40 μm (r1) from the wall of the arterioles averaged 35.5 Torr (74). Using Eq. 2 with boundary conditions P = P, at r = r̄, and P = $P_1$ at r = r2, we obtain the $J_o$ at r = r2.

$$J_o = \frac{K(P_o - P)}{r_1 \ln(r_1/r_o) + \frac{M(r^2_o - r^2_2)}{4r_2 \ln(r_1/r_o)} - M_r/2}$$

(18)

Taking r1 = r̄ + 40 μm and assuming values for rat brain cortex at K = $4.93 \times 10^{-10} \, \text{ml O}_2 \cdot \text{cm}^{-1} \cdot \text{Torr}^{-1} \cdot \text{s}^{-1}$, M = $8.34 \times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ (26), we obtain for these arterioles $J_o = (1.2–1.5) \times 10^{-5} \, \text{ml O}_2 \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$. Note that the Po values were measured only 3–4 μm from the lumen (the microelectrode was pressed against the wall). Thus values estimated above should lie between true $J_o$ and $J_o$.

Distribution of O2 consumption between vascular and parenchymal cells. It is instructive to delineate, on the basis of the results presented in Table 5, possible M vs. those in parenchyma. Swain and Pittman (67) estimated the tissue O2 consumption (Mtissue) in vivo on the basis of the O2 mass balance in the hamster retractor muscle to be $\sim 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$. Dutta et al. (14) estimated the rate at 3.63 $\times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ on the basis of in vitro polarographic measurements. These measurements indicated a spatially uniform O2 consumption as the electrode penetrated into the muscle; thus it is unlikely that vascular consumption was significantly different from the parenchymal cell consumption.

As a theoretical possibility we can consider a more general case. Mtissue can be estimated from the relationship

$$Mtissue = \phi M_{vase} + (1 - \phi) M_{parench}$$

(19)

where φ is the vascular volume fraction (strictly speaking, in estimates of φ the volume of blood has to be subtracted from the total tissue volume), Mvase is the vascular O2 consumption, and Mparench is the parenchymal O2 consumption. If the in vivo Mvase is similar to that of the parenchyma, then the estimates for the Mparench would not change from the value of $10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ (14, 67), since the vascular tissue content of most tissues is $\sim 5\%$ (77). However, if the Mvase is high, say 50% of Mmt, i.e., Mvase = $2.5 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, then applying Eq. 19 for φ = 0.05, we obtain Mtissue = $1.25 \times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, with Mparench = 0. Thus in this example the vascular wall consumes all of the O2. If we assume Mtissue = $10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, then Mparench = $0.53 \times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, i.e., 50% of the O2 is consumed by the vasculature and 50% by the parenchymal cells. This possibility, that a substantial fraction of O2 released from the arterioles is consumed within the vascular wall, was raised in Tsai et al. (71). However, polarographic measurements in several tissues (14) do not point to significant spatial nonuniformities of O2 consumption.

We can now consider existing experimental evidence of Mvase in vitro and in vivo and relate it to the consumption of Mparench. The data on vascular segments in vitro in Table 3 show that the values of O2 consumption in microvessels are generally higher than in large vessels, with the maximum value of $1.6 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ obtained for cerebral microvessels with succinate as substrate (66). Note that this value is below the Mmt.

In a series of papers, Clark and co-workers (77) reported a substantial increase of rat hindlimb M following vasoconstriction, and they initially attributed it to Mvase thus introducing the “hot pipes” concept. However, in subsequent publications the authors put forward alternative explanations of the results, including functional blood flow shunts and changes of muscle fiber metabolism (68, 69).

Marshall and Davies (44) found a 2.5-fold increase in M in hindlimbs of chronically hypoxic rats compared with normoxic control rats, from $0.7 \times 10^{-4}$ to $1.8 \times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$. On the basis of their results, using Eq. 19 and assuming that the entire increase in the organ consumption with stimulation is attributed to the vasculature and that a vascular volume fraction of 3.4% remains unchanged during the period of chronic hypoxia, one would estimate the difference between the Mvase for rats exposed to chronic hypoxia and normoxic controls to be $3.2 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$. An upper bound for the Mvase in the control case could be obtained by attributing the entire M to the vasculature ($2.1 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$). Then a lower and an upper bound for the Mvase in chronic hypoxia would be $3.2 \times 10^{-3}$ and $5.3 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, respectively.

Curtis et al. (11) showed that removing the endothelium in the dog hindlimb decreases hindlimb M by 35%. Assuming that the decrease is attributed entirely to the M and assuming the endothelium to be 1% of tissue volume, one would estimate the M to be $3.8 \times 10^{-3} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$ on the basis of the O2 uptake of the whole hindlimb of $1.1 \times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$.

Note that the above values (11, 44) are based on rather crude assumptions, the validity of which have not been demonstrated; thus the estimates have to be considered with extreme caution.

Tsai et al. (71) estimated Mvase of rat mesenteric to be $6.5 \times 10^{-2} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, with Mparench estimated directly from Po2 gradients at $2.4 \times 10^{-4} \, \text{ml O}_2 \cdot \text{ml}^{-1} \cdot \text{s}^{-1}$, i.e., the ratio of the consumption rates of $\sim 280$. Note that the estimated value of Mvase is 13 times higher than Mmt. If one assumes a vascular volume fraction of 5%, using the above numbers, one would conclude that the vasculature consumes 94% of the O2.
To summarize the evidence, the question of vascular 
$O_2$ consumption in vivo remains controversial. Additional experimental measurements are necessary to resolve this important question.

Possible reasons for the overestimation of intravascular flux. A common feature of all of the measurements listed in Table 4 is that the $J_i$ was estimated as the difference between convective inflow and outflow of $O_2$ in unbranched segments of microvessels, mostly arterioles. It is clear from Tables 5 and 6 that results from different laboratories, employing slightly different implementations of similar techniques, are quite consistent in that, apparently, they all, or at least most of them, yield overestimates of $J_i$. What are the possible reasons why such overestimates could be made?

The calculation of convective oxygen flow, $Q_{O2}^C$, at an intravascular site uses the following equation

$$Q_{O2}^C = \frac{\pi d^2}{4} v [Hb] \cdot C_p \cdot So_2$$  \hspace{1cm} (20)

where $d$ is the luminal diameter, $v$ is the RBC velocity averaged over the lumen, and $So_2$ is determined spectrophotometrically. Several assumptions are implicit in this calculation. They are axisymmetric flow in a vessel of circular cross-section and the appropriateness and accuracy of using values of $[Hb]$ and $So_2$ determined spectrophotometrically over the centerline of the vessel. A number of these assumptions have been evaluated previously (8, 15, 53), and most authors agree that each one falls short in one respect or another. For instance, the shape of the vessel lumen may not be circular; flow may not be axisymmetric and the calculation for the average velocity might not properly take into account the shape of the velocity profile; RBCs are unlikely to be uniformly distributed across the lumen, especially near a bifurcation; and $So_2$ is most likely nonuniform due to continuous diffusion of $O_2$ across the vessel wall. The microspectrophotometric techniques used to measure $[Hb]$ (42) and $So_2$ (54) provide average values along a narrow vertical path through the center of the vessel; the larger the nonuniformity in the luminal values, the less accurately these space-averaged numbers estimate the true luminal average. The $Po_2$ values measured in Ref. 71 may also be subject to this limitation. Since there should be steep $Po_2$ gradients within the lumen if there is a large $J_i$, the phosphorescence signal used to determine $Po_2$ must be analyzed using a method that takes such gradients into account (18). In addition, using $Po_2$ values to estimate $So_2$ in the steep part of the $O_2$ dissociation curve can give large uncertainties in predicted $So_2$. The RBC velocity in each case has been measured using an on-line photosensor and the cross-correlation technique of Wayland and Johnson (75).

The diffusive $J_i$ is calculated from the difference in convective fluxes at upstream and downstream sites, so that it is important to have accurate estimates of the latter fluxes. How could the $J_i$ be overestimated? If we suppose that the observed convective flux differs from the true flux by a systematic error, $\delta^C$, which could have a different magnitude at the two measurement sites, then the observed diffusive flux will overestimate the true diffusive flux if the systematic error at the upstream site is consistently larger than that at the downstream site. In this case we can express the observed diffusive flux ($J_{obs}$) relative to the true flux ($J_{true}$) as

$$\frac{J_{obs}}{J_{true}} = 1 + \left( \frac{\delta_{in}^C - \delta_{out}^C}{Q_{O2}^C} \right) \left( \frac{Q_{O2}^C}{J_{true}^C} \right)$$  \hspace{1cm} (21)

where ($\delta_{in}^C - \delta_{out}^C$) is the positive systematic error in $Q_{O2}^C$ and $L$ is the length of the vascular segment. Typically, the diffusive loss in $O_2$ amounts to only a 1–2% decrease in the convective $O_2$ flux, so that the term $Q_{O2}^C/ \left( J_{true}^C \right)$ in Eq. 21 should lie between 50 and 100. If the difference in systematic error of convective flux ($\delta_{in}^C - \delta_{out}^C$) in Eq. 21 is 5–10% of the true value, then the $J_{obs}$ could be an order of magnitude higher than the true value.

Why might a systematic error in convective $O_2$ flux be higher at the upstream end of an unbranched segment? Typically, the upstream site is close to the previous bifurcation, hence the luminal distribution of RBCs and RBC velocity profile might not have reached a stable configuration and the cross-sectional shape might not be circular. This could lead to a nonaxisymmetric distribution of velocity, $[Hb]$, and $So_2$ at the upstream site, so that the product of the factors derived from center-line measurements might not yield an accurate estimate of the true convective flux in Eq. 20.

The approach used to estimate $J_i$ relies on accurate values to calculate convective $O_2$ flux. High accuracy is especially critical in this approach, since the differences are typically small (~1%) relative to the values that are subtracted. Under the ideal controlled conditions of calibration, the accuracy of the methods used to determine the parameters of Eq. 20 is quite good, as shown previously by various investigators. However, when these methods are applied in vivo under conditions that can deviate substantially from those used in calibration studies, their accuracy is unknown and difficult to determine. It thus becomes important to search for the source(s) of systematic errors that could arise during in vivo applications of the methods used to measure velocity, $[Hb]$, and $So_2$. It appears likely then that a crucial aspect to consider is the impact of intravascular nonuniformities in luminal shape and velocity and in the distributions of RBCs, $So_2$, and $Po_2$ on the accuracy of estimates of $J_i$. If the assumptions inherent in the use of Eq. 20 are violated to a large enough degree, then it might be necessary to replace this simple expression with a more complicated, but more accurate, form in which the product of luminal distributions in velocity, $[Hb]$, and $So_2$ is integrated over the luminal cross-section. Full-diameter profiles of these variables have been reported (15), but the analysis of these profiles has not progressed to the point where luminal variations (i.e., radial dependencies in an axisymmetric situation) can be determined with confidence. It appears that future progress in this area will require that the existing methods be further developed to include information that can be inter-
interpreted in terms of intravascular profiles or that methods requiring less restrictive assumptions than those listed above must be developed and/or applied (e.g., use of fluorescently-labeled RBCs for RBC flow determination).

It is important to emphasize that the above arguments apply only to determinations of \( J_i \) in unbranched segments that require subtraction of nearly equal quantities. The values of \( S_2 \) and \( P_2 \) measured at different locations along the microvasculature, as reported by numerous researchers (12, 27, 38, 39, 54, 67, 71), that represent significant precapillary \( O_2 \) transport are not in question.

**Conclusions.** In vitro experiments on endothelial and smooth muscle cell suspensions and vascular segments show that \( M \) of the vessel wall does not exceed the estimated \( M_{m} \) of \( 5 \times 10^{-3} \) ml \( O_2 \) · ml\(^{-1} \) · s\(^{-1} \). Consideration of \( M \) via a NO-related pathway does not qualitatively change this conclusion. However, some in vivo data based on measurements of \( S_2 \) or \( P_2 \) gradients in unbranched segments yield values that are significantly higher than \( M_{m} \) by an order of magnitude or more. A possibility remains that some other extramitochondrial pathways are associated with \( O_2 \) utilization that is of the same order of magnitude higher than \( M_{m} \). Further analysis is necessary to estimate \( O_2 \) utilization in known pathways. However, as we have shown, high values of \( J_i \) may be inconsistent with certain measurements of transvascular \( P_2 \) difference. The likely place to look for the source of discrepancy is in the microcirculatory measurements in arterioles. All measurements in the arterioles use similar techniques; the interpretation of these measurements, such as the neglect of nonuniform velocity, [Hb], and \( S_2 \), and possibly the vascular wall \( K \) may need to be reconsidered. It is important to note that capillary measurements do not suffer from the same potential artifacts due to the single-file nature of flow and give reasonable values of \( O_2 \) flux.

**APPENDIX**

**Derivation of the two-layer model.** We formulated the two-layer model in which the vascular wall is represented as two separate layers: an endothelial cell layer and a smooth muscle cell layer. For a given vascular wall, the endothelial cell layer is assumed to be \( \sim 0.5 \) μm thick, with the rest modeled as the smooth muscle layer. \( K \) and \( M \) are different in each layer. The \( P_2 \) profile and flux are assumed to be continuous across the endothelial cell and smooth muscle cell interface.

Similar to the one-layer model, the governing equation of diffusion in the endothelial cell layer, can be represented as

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_e}{\partial r} \right) - \frac{M_e}{K_e} = 0 \quad (A1)
\]

where \( P_e \) is the \( P_2 \) in the endothelial cell layer, and \( M_e \) and \( K_e \) are the \( O_2 \) consumption rate and the Krogh coefficient, respectively, in the endothelial cell layer.

The corresponding diffusion equation for the smooth muscle cell layer is

\[
\frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial P_s}{\partial r} \right) - \frac{M_s}{K_s} = 0 \quad (A2)
\]

where \( P_s \) is the \( P_2 \) in the smooth muscle cell layer and \( M_s \) and \( K_s \) are the \( O_2 \) consumption rate and the Krogh coefficient, respectively, in the smooth muscle cell layer.

The boundary conditions are

\[
r = r_i \quad P_e = P_i \quad (A3)
\]

where \( r_i \) is the radius and \( P_i \) is the \( P_2 \) at the luminal side of the endothelial cell layer

\[
r = r_o \quad P_s = P_o \quad (A4)
\]

where \( r_o \) is the radius and \( P_o \) the \( P_2 \) at the outside of the smooth muscle cell layer, and

\[
r = r_m \quad P_e = P_s, \quad K_e \frac{\partial P_e}{\partial r} = K_s \frac{\partial P_s}{\partial r} \quad (A5)
\]

where \( r_m \) is the radius of the interface between the endothelial and smooth muscle cell layers.

Applying these boundary conditions, we get

\[
P_i = \frac{M_e r_i^2}{4K_e} + A_1 \ln(r_i) + A_2, \quad P_o = \frac{M_s r_o^2}{4K_s} + A_3 \ln(r_o) + A_4 \quad (A6)
\]

\[
A_1 = \left[ (P_e - P_i) + \frac{M_e r_i^2}{4K_e} - \frac{M_s r_o^2}{4K_s} \right] + \frac{(M_e - M_s) r_m^2 \ln(r_m/r_o)}{2K_s} - \frac{M_e}{K_e} \frac{M_s}{K_s} \frac{r_m^3}{4}
\]

\[
\ln(r_m/r_i) + \frac{K_e \ln(r_m/r_o)}{K_s} \quad (A7)
\]

where

\[
A_2 = \left( P_i - \frac{M_e r_i^2}{4K_e} \right) - A_1 \ln(r_i) \quad (A8)
\]

\[
A_3 = \frac{(M_e - M_s) r_m^2}{2K_s} + A_1 \frac{K_e}{K_s} \quad (A9)
\]

\[
A_4 = r_m^2 \left[ \frac{M_e}{K_e} - \frac{M_s}{K_s} - \frac{2(M_e - M_s) \ln(r_m)}{2K_s} \right] + A_1 \left( 1 - \frac{K_e}{K_s} \right) \ln(r_m) + A_2 \quad (A10)
\]

\[
J_i \text{ is expressed as} \quad J_i = -K_e \frac{\partial P_e}{\partial r} \bigg|_{r = r_i} = -\left( \frac{M_e r_i}{2} + A_1 \frac{K_e}{r_i} \right) \quad (A11)
\]
Similarly $J_o$ is obtained as

$$J_o = -K_o \frac{\partial P_o}{\partial r} \bigg|_{r=r_o} = \left( \frac{M_o r_o}{2} + A_3 \frac{K_o}{r_o} \right) \tag{A12}$$

Substituting the value of $A_1$ in Eq. A7 into Eq. A11, we obtain

$$P_o = P_i - \frac{(J_{ci} r_i + M_o r_o^2)}{2K_o} \ln \frac{r_i}{r_o} + \frac{M_e}{4K_o} (r_i^2 - r_o^2) + \frac{M_o}{4K_o} (r_o^2 - r_i^2) + \frac{M_e}{2K_o} (r_o^2 - r_i^2) - \frac{(M_e - M_o) r_o^2}{2K_o} \ln \frac{r_o}{r_i} \tag{A13}$$

This gives the $P_o$ for a given $J_i$ and $P_i$. The $P_o_{\text{min}}$ can be obtained by setting $M_o$ to 0 in Eq. A13. If the value of $P_o$ turns out to be negative, a value that is not physiologically possible, we have $P_o_{\text{min}} < 0$. We obtain $M_{e\text{min}}$ by setting $P_o$ to 0 and solving for $M_e$ in Eq. A13.

To get the $P_o_{\text{max}}$ and $P_o_{\text{max}}$ we impose a no-flux condition ($J_i = 0$) on the outer vessel wall in Eq. A12. Substituting the value of $A_2$ into Eq. A12 for $J_o = 0$, we get

$$P_o = P_i - \frac{(J_{ci} r_i + M_o r_o^2)}{2K_o} \ln \frac{r_i}{r_o} + \frac{M_e}{4K_o} (r_i^2 - r_o^2) + \frac{M_o}{4K_o} (r_o^2 - r_i^2) + \frac{M_e}{2K_o} (r_o^2 - r_i^2) - \frac{(M_e - M_o) r_o^2}{2K_o} \ln \frac{r_o}{r_i} \tag{A14}$$

Eq. A14 corresponds to the case of maximum wall consumption rate, and solving it with Eq. A13 gives us $P_o_{\text{max}}$ and $M_e_{\text{max}}$.

Hence, the different cases for $M_e$ and $P_o$ can be summarized as Case 1

$$0 \leq M_e \leq M_{e\text{max}} \quad \text{and} \quad P_o_{\text{min}} \leq P_o \leq P_o_{\text{max}}$$

and Case 2

$$M_{e\text{min}} < M_e \leq M_{e\text{max}} \quad \text{and} \quad 0 < P_o \leq P_o_{\text{max}}$$

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