Oxygen transport across vasa recta in the renal medulla

WENSHENG ZHANG AND AURÉLIE EDWARDS
Department of Chemical and Biological Engineering, Tufts University, Medford, Massachusetts 02155

Received 31 January 2002; accepted in final form 10 May 2002

Zhang, Wensheng, and Aurélie Edwards. Oxygen transport across vasa recta in the renal medulla. Am J Physiol Heart Circ Physiol 283: H1042–H1055, 2002.—In this model of oxygen transport in the renal medullary microcirculation, we predicted that the net amount of oxygen reabsorbed from vasa recta into the interstitium is on the order of $10^{-4}$ mmol/s, i.e., significantly lower than estimated medullary oxygen requirements based on active sodium reabsorption. Our simulations confirmed a number of experimental findings. Low medullary $P_{O_2}$ results from the countercurrent arrangement of vessels and an elevated vasa recta permeability to oxygen, as well as high metabolic needs. Diffusional shunting of oxygen between descending vasa recta (DVR) and ascending vasa recta also explains why a 20-mmHg decrease in initial $P_{O_2}$ at the corticomedullary junction only leads to a small drop in papillary tip $P_{O_2}$ (<2 mmHg with baseline parameter values). Conversely, small changes in the consumption rate of DVR-supplied oxygen, in blood flow rate, in hematocrit, or in capillary permeability to oxygen, beyond certain values sharply reduce interstitial $P_{O_2}$. Without erythrocytes, papillary tip $P_{O_2}$ cannot be maintained above 10 mmHg, even when oxygen consumption is zero.

IN THE MAMMALIAN KIDNEY, the partial pressure of oxygen ($P_{O_2}$) is ~50 mmHg in the cortex but only 10–20 mmHg in the medulla (5, 23, 29). Low medullary $P_{O_2}$ is a consequence of high metabolic requirements and the countercurrent arrangement of vessels that nourish and drain the outer (OM) and inner medulla (IM). The active reabsorption of water and solutes by nephron loops requires significant energy, and many investigators have attempted to relate active solute reabsorption to oxygen consumption in the renal medulla (3, 17).

As blood flows down toward the tip of the medulla, most of the oxygen that it carries diffuses across descending vasa recta (DVR) walls to the interstitium. It can then either diffuse to the surrounding tubules, where it is consumed for active transport processes, or be reabsorbed into ascending vasa recta (AVR) and carried back to the cortex. Oxygenation of the medulla is therefore limited by the diffusional shunting of oxygen between DVR and AVR. If medullary blood flow were higher, thus supplying more oxygen, it would tend to dissipate corticomedullary osmolality gradients. However, too little oxygen can cause medullary hypoxic injury, which is characterized by tubular necrosis (7). A careful balance between the supply and demand of oxygen is therefore essential.

Isolated kidney perfusion with a red blood cell (RBC)-free medium causes severe lesions in the medullary thick ascending limb (mTAL) of Henle's loop (1) and the proximal straight tubule (33). Necroses in both segments can be prevented by the addition of erythrocytes or hemoglobin to the perfusion fluid (8, 33). In the presence of RBCs, mild hypoxia leads to widespread proximal tubule (PT) damage, whereas the thick ascending limb is spared; it is thought that the high oxygen affinity of hemoglobin in erythrocytes competes with the diffusional shunt of oxygen, thereby limiting the radial transfer of oxygen from DVR to AVR and allowing more oxygen to be transported deeper in the medulla (15). PT injury occurring even when the perfusate contains RBCs may result from preglomerular shunting of oxygen within the cortical vasculature (32).

In this study, we extended our previous mathematical model of the medullary microcirculation (36) to account for oxygen transport and to explore the effects of changes in supply (i.e., blood flow, hematocrit) and demand (i.e., consumption rate) on medullary $P_{O_2}$. Agreement between theoretical results and experimental observations confirmed the validity of our approach.

MATHEMATICAL MODEL

Fundamental Conservation Equations

The fundamental assumptions of our model of renal medullary microvascular transport have been extensively described earlier (11–13, 36) and are briefly summarized below.

In our model, we only consider those vasa recta that are destined for the IM, i.e., those that lie in the center of the vascular bundles and do not perfuse the capillary plexus in the OM. Plasma and RBCs are considered separately. The RBC membrane is only permeable to water, urea, and oxygen. As blood flows down along DVR and then back to the cortex along AVR, DVR and AVR exchange water, NaCl, urea, proteins, and oxygen with each other through the interstitium. In addition to the nonselective paracellular pathway across vessel walls, AQP-1 water channels, which are present in DVR only, constitute a transcellular pathway.
for water exclusively. Specific urea transporters have also been observed in DVR walls. The deposition of NaCl, urea, and water from the loops of Henle and the collecting ducts into the IM interstitium is accounted for by interstitial generation rates that undergo spatial variation. In the OM, exchanges occur only between the vasa recta and the interstitium because DVR and AVR form vascular bundles from which nephron loops are excluded, so that generation rates are taken to be zero. Proteins in the interstitium are assumed to come exclusively from vasa recta, and, as shown recently, concentration polarization effects can be neglected (36).

Our model of the renal medullary microcirculation consists of a series of conservation equations in plasma, RBCs, and the interstitium. If x is the axial coordinate along the corticomedullary axis, conservation of volume in plasma and RBCs can be expressed as

\[
\frac{dQ^P}{dx} = \pm(j_v - \Gamma j_P^R) N \pi D + \left(\frac{Q^P}{N}\right) \frac{dN}{dx} \quad (1)
\]

\[
\frac{dQ^R}{dx} = \pm \Gamma j_P^R N \pi D + \left(\frac{Q^R}{N}\right) \frac{dN}{dx} \quad (2)
\]

where \(Q^P\) and \(Q^R\) are the plasma and RBC flow rates, respectively, and \(j_v\) and \(j_P^R\) are the volume fluxes (per unit membrane area) across the capillary wall and the RBC membrane, respectively. The parameter \(\Gamma\) represents the cell-to-vessel surface area ratio, \(N\) denotes the number of vessels, \(D\) is the vessel diameter, and + and − apply to AVR and DVR, respectively. Because the RBC membrane is impermeable to NaCl and proteins, conservation of NaCl and proteins in plasma gives

\[
\frac{d(Q^P c_i^P)}{dx} = \pm j_u + j_{uc} - \Gamma j_P^R N \pi D + \left(\frac{Q^P c_i^P}{N}\right) \frac{dN}{dx} \quad (3)
\]

where \(j_u\) and \(j_{uc}\) are the paracellular and carrier-mediated transcapillary molar fluxes of urea, respectively (\(j_{uc}\) is zero in AVR), and \(j_P^R\) is the molar flux of urea across RBCs.

The RBC concentration of urea (\(c_i^R\)) can be obtained from the following conservation equation

\[
\frac{d(fQ^R c_i^R)}{dx} = \pm \Gamma j_P^R N \pi D + \left(\frac{fQ^R c_i^R}{N}\right) \frac{dN}{dx} \quad (5)
\]

where \(f\) is the fractional volume of distribution of urea within RBCs, taken to be 0.86.

Conservation of hemoglobin and other nonurea solutes (e.g., potassium, magnesium, and associated intracellular anions) in RBCs yields

\[
\frac{d(Q^R c_i^R)}{dx} = \pm \left(\frac{Q^R c_i^R}{N}\right) \frac{dN}{dx} \quad (6)
\]

where \(c_i^R\) is the RBC concentration of solute \(i\). Order of magnitude analysis suggests that axial diffusion in the interstitium is negligible relative to radial transport. Conservation of volume, NaCl, urea, and proteins in the interstitium can thus be written as

\[
[J_i(x)N(x)\pi D]_{DVR} + [J_i(x)N(x)\pi D]_{AVR} + A_{uc}(x)\psi_u(x) = 0 \quad (7)
\]

\[
[J_{Na}(x)N(x)\pi D]_{DVR} + [J_{Na}(x)N(x)\pi D]_{AVR} + A_{uc}(x)\psi_Na(x) = 0 \quad (8)
\]

\[
[J_v(x) + J_{uc}(x)]N(x)\pi D]_{DVR} + [J_v(x)N(x)\pi D]_{AVR} + A_{uc}(x)\psi_v(x) = 0 \quad (9)
\]

\[
[J_{pr}(x)N(x)\pi D]_{DVR} + [J_{pr}(x)N(x)\pi D]_{AVR} = 0 \quad (10)
\]

where \(A_{uc}\) is the cross-sectional area of the medullary interstitium; \(J_{Na}\) is molar flux of sodium; and \(\psi_v\), \(\psi_Na\), and \(\psi\) are the local generation rates of volume, sodium, and urea, respectively, per unit area of interstitium, which simulate deposition from the loops of Henle and the collecting ducts. The latter three terms are taken to be zero in the outer medulla, as described above. Solving these four equations yields the interstitial values of the hydraulic pressure and the concentration of NaCl, urea, and proteins.

As described earlier, two different pathways for water exist in DVR. Hence, in Eq. 1, \(J_v\) is the sum of two contributions, the paracellular (\(J_{vp}\)) and transcellular (\(J_{vt}\)) volume fluxes, which are given by

\[
J_{vp} = L_p[\Delta P - \sigma_p \Delta P_{pr} - RT \sum_i \sigma_i \gamma_i(C_i^p - C_i^l)] \quad (11)
\]

\[
J_{vt} = L_v[\Delta P - \Delta P_{pr} - RT \sum_i \gamma_i(C_i^p - C_i^l)] \quad (12)
\]

where \(L_p\) and \(L_v\) represent the hydraulic conductivities of the paracellular and transcellular pathways, respectively; \(\Delta P\) is the transcapillary hydraulic pressure difference; \(\Delta P_{pr}\) is the transcapillary oncotic pressure difference due to plasma proteins; \(R\) is the gas constant; \(T\) is temperature; and \(\sigma_{pr}\) is the reflection coefficient of the paracellular pathway to protein. The interstitial concentration and the activity coefficient of solute \(i\) are denoted by \(C_i^l\) and \(\gamma_i\), respectively, and \(\sigma_i\) is the reflection coefficient of the paracellular pathway to solute \(i\). Note that the reflection coefficients are taken to be one for the solute-impermeable transcellular pathway and that \(J_{vt}\) is zero across AVR, where no AQp-1 water channels have been found. The volume flux across the RBC membrane (\(J_{pr}^R\)) is given by

\[
J_{pr}^R = L_R[\Pi_{pr} - \Pi_{lb} - RT \sum_i \gamma_i(C_i^k - C_i^l)] \quad (13)
\]

where \(L_R\) is the RBC membrane hydraulic conductivity and \(\Pi_{pr}\) and \(\Pi_{lb}\) are the oncotic pressures due to plasma proteins and to hemoglobin in the cells, respectively.

The paracellular flux of solute \(i\) (\(i = \text{sodium, protein, or urea}\)) across capillary walls can be written as

\[
J_i = J_{vp} (1 - \sigma_i) \frac{C_i^p - C_i^l \exp(-Pe)}{1 - \exp(-Pe)} \quad (14)
\]

\[
P_e = \frac{J_{vp}(1 - \sigma_i)}{P_i} \quad (15)
\]

where \(P_i\) is the permeability of vessel to solute \(i\) and the Peclet number (\(Pe\)) is a measure of the importance of convection relative to diffusion. The carrier-mediated transcapillary and transmembrane fluxes of urea, respectively, are given by

\[
J_{uc} = P_{uc}(C_{uc}^k - C_{uc}^l) \quad (16)
\]

\[
J_{pr}^u = P_{pr}^u(C_{pr}^k - C_{pr}^l) \quad (17)
\]
A multiunit model is derived in APPENDIX A. Osmotic pressures, vessel numbers, and the cross-sectional area of the interstitium are calculated as described in Zhang and Edwards (36). Table 1 summarizes the baseline values used in our transport simulations.

**Oxygen Transport Equations**

In this study, the model is extended to include renal medullary oxygen transport. A large portion of oxygen is carried by blood as oxyhemoglobin, that is, oxygen chemically binds to hemoglobin. In RBCs, the dissociation of oxyhemoglobin to O$_2$ and hemoglobin can be expressed as the simple one-step reaction

$$\text{HbO}_2 \Leftrightarrow \text{Hb} + \text{O}_2$$

where Hb represents one of the four heme groups in each hemoglobin molecule. According to this notation, C$_{\text{HbO}_2}$ is four times the concentration of oxyhemoglobin and C$_{\text{Hb}}$ is four times that of deoxyhemoglobin.

If $R$ is the net amount of O$_2$ released from the reaction above (in mmol·s$^{-1}·$cm$^{-1}$), conservation equations for O$_2$, Hb, and HbO$_2$ in RBCs within a single vas rectum can be written as

$$\frac{d(qR C_{\text{HbO}_2})}{dx} = -J_{O_2}^R \Gamma \pi D + R$$ (18)

$$\frac{d(qR C_{\text{Hb}})}{dx} = R$$ (19)

$$\frac{d(qR C_{\text{HbO}_2})}{dx} = -R$$ (20)

where C$_{\text{RbO}_2}$, C$_{\text{Hb}}$, and C$_{\text{HbO}_2}$ are the RBC concentrations of O$_2$, Hb, and HbO$_2$, respectively; q$^R$ is the single vessel flow rate of RBCs; and $J_{O_2}^R$ is the transmembrane flux of oxygen per unit membrane area. The flow rate is considered here in a single vessel to simplify subsequent derivations.

Several investigators (9, 24) studied oxygen transport resistance and oxyhemoglobin dissociation kinetics and concluded that the dissociation is much faster than the diffusion of oxygen, so that the reaction appears to be at equilibrium. In this case, the saturation (S) is given by the classic Hill equation

$$S = \frac{C_{\text{HbO}_2}}{C_{\text{HbO}_2} + C_{\text{Hb}}} = \frac{(C_{\text{O}_2}/C_{\text{O}_2}^n)^n}{1 + (C_{\text{O}_2}/C_{\text{O}_2}^n)^n}$$ (21)

where C$_{\text{O}_2}$ and n are equilibrium parameters obtained from experimental data. This equation can be used to eliminate the unknown R in Eqs. 18–20. As derived in APPENDIX B, we have

$$C_{\text{O}_2} \frac{dqR}{dx} + C_{\text{O}_2} \frac{dC_{\text{Hb}}}{dx} \left[ 1 + \frac{n (C_{\text{O}_2}/C_{\text{O}_2}^n)^n (C_{\text{HbO}_2} + C_{\text{Hb}})}{1 + (C_{\text{O}_2}/C_{\text{O}_2}^n)^n} \right] = -J_{O_2}^R \Gamma \pi D$$ (22)

Because the RBC membrane is impermeable to hemoglobin, the total mass flow of heme (Hb + HbO$_2$) in a single vas rectum remains constant. By adding Eqs. 19 and 20, we have

$$\frac{d(qR C_{\text{Hb}})}{dx} = 0$$ (23)

Table 1. **Parameter values for the basic model**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transport parameters</strong></td>
<td></td>
</tr>
<tr>
<td>L$_{\text{DVR}}$, cm$^{-1}$·mmHg$^{-1}$</td>
<td>1.8 × 10$^{-6}$</td>
</tr>
<tr>
<td>AVR</td>
<td>12.5 × 10$^{-6}$</td>
</tr>
<tr>
<td>L$_{\text{DVR}}$, cm$^{-1}$·mmHg$^{-1}$</td>
<td>1.0 × 10$^{-7}$</td>
</tr>
<tr>
<td>AVR</td>
<td>1.0 × 10$^{-7}$</td>
</tr>
<tr>
<td>Paracellular permeability to sodium, cm/s</td>
<td>75 × 10$^{-5}$</td>
</tr>
<tr>
<td>AVR</td>
<td>113 × 10$^{-5}$</td>
</tr>
<tr>
<td>Paracellular permeability to urea, cm/s</td>
<td>75 × 10$^{-5}$</td>
</tr>
<tr>
<td>AVR</td>
<td>113 × 10$^{-5}$</td>
</tr>
<tr>
<td>Paracellular permeability to proteins, cm/s</td>
<td>1 × 10$^{-7}$</td>
</tr>
<tr>
<td>AVR</td>
<td>1 × 10$^{-6}$</td>
</tr>
<tr>
<td>Paracellular reflection coefficient to proteins</td>
<td>0.89</td>
</tr>
<tr>
<td>AVR</td>
<td>0.70</td>
</tr>
<tr>
<td>Activity coefficient of sodium*</td>
<td>1.86</td>
</tr>
<tr>
<td>AVR</td>
<td>1.86</td>
</tr>
<tr>
<td>Activity coefficient of urea</td>
<td>0.9</td>
</tr>
<tr>
<td>AVR</td>
<td>0.9</td>
</tr>
<tr>
<td>Activity coefficient of nonurea solutes in RBCs</td>
<td>0.9</td>
</tr>
<tr>
<td>AVR</td>
<td>0.9</td>
</tr>
<tr>
<td>Physical dimensions</td>
<td></td>
</tr>
<tr>
<td>D, μm</td>
<td>15.6</td>
</tr>
<tr>
<td>AVR</td>
<td>20.0</td>
</tr>
<tr>
<td>Total length of the medulla, mm</td>
<td>7.8</td>
</tr>
<tr>
<td>Length of the inner medulla, mm</td>
<td>5.9</td>
</tr>
</tbody>
</table>

**Boundary conditions**

Initial values
- Single vessel blood flow rate, nl/min: 9
- Hematocrit: 0.25
- Plasma protein concentration, g/dl: 6.8
- Sodium plasma concentration, mmol/l: 150
- Urea plasma concentration, mmol/l: 5
- Urea RBC concentration, mmol/l: 5
- Hemoglobin RBC concentration, mmol/l: 5.1
- RBC concentration of nonurea solutes, mmol/l: 292
- Whole kidney glomerular filtration rate, μl/min: 784

Values were obtained from Refs. 12 and 13. Initial values reflect those at the corticomedullary junction in descending vasa recta (DVR). AVR, ascending vasa recta; L$_{\text{DVR}}$, paracellular hydraulic conductivity; L$_{\text{DVR}}$, transcellular osmotic hydraulic conductivity; L$_{\text{DVR}}$, hydraulic conductivity of red blood cell (RBC) membrane; P$_{\text{ur}}$, carrier-mediated permeability of capillary wall to urea; P$_{\text{ur}}$, carrier-mediated permeability of RBC membrane to urea; D, diameter. *Value of the activity coefficient is taken as twice that for sodium to implicitly account for chloride in the osmotic pressure term.
where $C_{\text{Hb}}^{\text{R}} = C_{\text{Hb}}^1 + C_{\text{HbO}_2}$ and denotes the total (i.e., oxy plus deoxy) heme concentration.

These two conservation equations can be rewritten in terms of the overall RBC volume flow rate ($Q^R$) as follows

$$\frac{dQ^R}{dx} \left[ 1 + n \frac{(C_{O_2}^R / C_{\text{Hb}}^{\text{R}})Q^R_{\text{CHbT}}}{(C_{O_2}^R/C_{\text{Hb}}^{\text{R}})^2} \right]$$

$$= - \frac{1}{Q^R} \left( J_{O_2}^R \Gamma N \pi D + C_{O_2}^R \frac{dQ^R}{dx} \right) + \frac{C_{O_2}^R}{N} \frac{dN}{dx} \tag{24}$$

Conservation of oxygen in plasma can also be expressed as

$$\frac{d(Q^P C_{O_2}^P)}{dx} = - (J_{O_2}^P - \Gamma J_{O_2}^P N \pi D) \frac{Q^P C_{O_2}^P}{N} \frac{dN}{dx} \tag{26}$$

where $C_{O_2}^P$ is the plasma concentration of oxygen and $J_{O_2}^P$ is the transcapillary flux of oxygen.

Because the permeability of the RBC cytosol-membrane interface to oxygen and that of the plasma-capillary wall interface are high (that is, higher than 0.01 cm/s, as described below), and the transcapillary volume flow is consistently $\approx 2 \times 10^{-4}$ cm/s, the Peclet number is smaller than $2 \times 10^{-2}$. Oxygen transport is therefore dominated by diffusion, and convection can be neglected. Hence, $J_{O_2}^P$ and $J_{O_2}^R$ are written as

$$J_{O_2}^P = P_{O_2}^P \left( C_{O_2}^P - C_{O_2}^I \right) \tag{27}$$

$$J_{O_2}^R = P_{O_2}^R \left( C_{O_2}^R - C_{O_2}^I \right) \tag{28}$$

where $P_{O_2}^P$ and $P_{O_2}^R$ are the permeabilities of the RBC cytosol-membrane interface and the plasma-capillary wall interface to oxygen, respectively (hereafter referred to as the permeability of RBC membrane and capillary wall, respectively), and $C_{O_2}^I$ is the interstitial oxygen concentration.

Equations 24–26 are integrated along vasa recta, along with the other conservation equations described above, to obtain $C_{O_2}^{AVR}$, $C_{\text{Hb}}^{\text{R}}$, and $C_{O_2}^{\text{R}}$. The Hill equation (Eq. 21) can then be used to obtain the values of $C_{\text{Hb}}^1$ and $C_{\text{HbO}_2}$.

Conservation of oxygen in the interstitium is given by an equation similar to that for other solutes

$$[J_{O_2}^P(x) N(x) \pi D]_{\text{DVR}} + [J_{O_2}^R(x) N(x) \pi D]_{\text{AVR}} + A_{\text{int}} r_{O_2} = 0 \tag{29}$$

where $r_{O_2}$ is the volumetric consumption rate of oxygen supplied by vasa recta (in mmol·s⁻¹·cm⁻²), that is, the local net amount of oxygen reabsorbed from the microcirculation into the interstitium.

Flow rates and concentrations in plasma and RBCs are obtained by integrating along the corticomedullary axis the set of ordinary differential equations (Eqs. 1–6 and 24–26), which are solved using Gear’s method. Interstitial concentrations and pressures are calculated at every depth by solving nonlinear equations (Eqs. 7–10 and 29) with a modified Powell hybrid method. Because all the variables in DVR and AVR are highly coupled and boundary values for AVR are not known at the beginning, profiles for all the variables in AVR are assumed initially, and integration around the countercurrent loops is iterated until convergence is achieved. The procedure is described in more detail by Zhang and Edwards (36).

**Parameter Selection**

**Medullary Oxygen Tension**

It is not surprising that a wide range of cortex and medullary PO$_2$ measurements has been reported, given the large gradient of PO$_2$ along the corticomedullary axis. With the use of microelectrodes in anesthetized dogs, Aperin (2) found that PO$_2$ averaged 47 mmHg in the cortex, 36 mmHg in the outer medulla, and 4.3 mmHg in the inner medulla. Leichtweiss et al. (19) reported that medullary PO$_2$ was in the range of 10–11 mmHg in rats. In the study by Rosen et al. (29), PO$_2$ in the rat kidney ranged from 50 to 54 mmHg in the cortex and was as low as 19 mmHg in the medulla. In another experiment, Dinour et al. (10) inserted sensitive Clark-type O$_2$ microelectrodes into the kidney of anesthetized rats and reported that cortical PO$_2$ ranged from 60 to 68 mmHg, whereas medullary PO$_2$ ranged from 14 to 21 mmHg. In yet another study, Brezis et al. (5) measured PO$_2$ of ~30 mmHg between 0 and 1 mm below the OM and 20 mmHg between 1 and 2 mm below that. The recent data of Liss et al. (23) suggest that PO$_2$ varies from 16 to 40 mmHg in the medulla and from 38 to 46 mmHg in the cortex. Taken together, these measurements suggest that PO$_2$ ranges from 40 to 70 mmHg in the cortex, 30 to 50 mmHg in the outer medulla, and then drops to perhaps as low as 4 to 10 mmHg near the papillary tip. Summarized in Fig. 1 are reported oxygen levels in different anatomic zones of the medulla.

PO$_2$ has not been determined precisely at the corticomedullary junction. Given the range of reported values in both the cortex and OM, we varied PO$_2$ in DVR at the corticomedullary junction between 45 and 65 mmHg, with a baseline value of 55 mmHg.

**Permeability of Oxygen through Vasa Recta**

To avoid the difficulty of distinguishing the effects of a membrane and its boundary layer, and given the lack of data regarding transport parameters, we opted to lump together the resistance of a given barrier and that of the adjacent boundary layer. We thus considered two mass transfer coefficients, one corresponding to the RBC cytosol-membrane interface [referred to as RBC permeability ($P_{O_2}^P$)], and the other one corresponding to the plasma-capillary wall interface [referred to as wall permeability ($P_{O_2}^W$)]. The total intraluminal resistance can then be expressed as

$$h = \frac{1}{P_{O_2}^P} = \frac{1}{P_{O_2}^R} + \frac{1}{P_{O_2}^W} \tag{30}$$

where $P_{O_2}^P$ is the (overall) capillary permeability to oxygen.

Hellums et al. (18) compared the resistance of homogeneous oxyhemoglobin solutions in plasma to that of RBCs in blood with the same total oxyhemoglobin concentration and found that the fractional resistance in the capillary was ~20% in the former case and 50% in the latter one. Assuming that the resistance outside the capillary remains the same in both situations, the resistance of RBCs is found to represent 75% of the total intracapillary resistance, i.e., the ratio of $P_{O_2}^W$ to $P_{O_2}^R$ is equal to 3. To account for the disturbance effects of RBCs in plasma, we varied the ratio of $P_{O_2}^W$ to $P_{O_2}^P$ from 1 to 5 in our simulations below.

In their review, Hellums et al. (18) also estimated that Nusselt numbers (Nu) vary between 2.1 and 2.4 and between 2.5 and 3.3 for capillaries 15 and 20 μm in diameter, respectively. On the basis of their definition of Nu, this means that PO$_2$ ranges from 0.027 to 0.036 cm/s in DVR and from 0.030 to 0.035 cm/s in AVR. In another study, Eggleton et al. (14)
predicted that $P_{O_2}$ lies between 0.05 and 0.13 cm/s if the hematocrit is comprised between 25% and 50%. The investigators also found that capillary radius has little effect on $P_{O_2}$ due to the disturbance effects of RBCs in plasma, so that oxygen transfer resistance is primarily located in the boundary layers of the capillary wall and RBC membrane. We thus varied vasa recta $P_{O_2}$ between 0.001 and 0.1 cm/s.

Medullary Oxygen Consumption Rate

Many studies have demonstrated a direct correlation between active sodium reabsorption and oxygen consumption in the kidney. Sodium reabsorption occurs along the entire nephron. Moe et al. (25) estimated that, in the rat, 60% of the filtered sodium is reabsorbed in the PT, 30% in the mTAL, 7% in the distal convoluted tubule, and 3% in the collecting duct. Only the thick ascending limb and the S3 segment of the PT are located in the OM, the rest being in the cortex. Gullans (17) suggested that there exists a fixed stoichiometric ratio between sodium reabsorption and oxygen consumption in given nephron segments. The investigator estimated that 18 meq sodium are reabsorbed for each molecule of oxygen consumed in distal tubules and that the corresponding ratios are 24:1 to 30:1 in PTs and 36:1 in mTALs.

**Oxygen consumption rate by TALs and PTs.** The filtered load of sodium has been estimated as $2 \mu$mol/s in rats (11). If the fraction of sodium reabsorbed by mTALs is taken to be 30% and the stoichiometric ratio in mTALs is equal to 36 (see above), the oxygen consumption rate for mTAL sodium reabsorption is calculated to be $1.7 \times 10^{-5}$ mmol/s. A similar approach yields $5.0 \times 10^{-5}$ mmol/s for PT sodium reabsorption. Because only the S3 segment is situated in the OM, however, this estimate represents an upper limit. Overall, these calculations suggest that active sodium reabsorption in the OM requires between 2 and $7 \times 10^{-5}$ mmol/s of oxygen.

**Total oxygen consumption rate in the renal medulla.** A distribution of oxygen consumption in various segments of the kidney can be found in the review of Gullans (17). Accounting for both ouabain-insensitive (i.e., basal) and ouabain-sensitive metabolism, his data indicate that 30% of oxygen is consumed in the OM and 5% is consumed in the IM. In separate studies, Endre et al. (15) and Shapiro et al. (30) measured the oxygen consumption rate in the rat kidney as $8 \mu$mol/min, i.e., $1.3 \times 10^{-4}$ mmol/s. Hence, the oxygen consumption rate is estimated as $4.0 \times 10^{-5}$ mmol/s in the OM and $6.7 \times 10^{-6}$ mmol/s in the IM. Both this calculation and the one above based on active sodium reabsorption suggest that the overall oxygen consumption rate in the renal medulla is on the order of $10^{-5}$ mmol/s.

**Oxygen supply by DVR blood flow.** The amount of oxygen supplied to the medulla by blood flow can be estimated as follows. Assuming that the initial $P_{O_2}$ in DVR blood flow is 55 mmHg, using the Hill equation (Eq. 21) and parameter values given in Tables 1 and 2, we calculate that the total

<table>
<thead>
<tr>
<th>Table 2. Oxygen transport parameter values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
</tr>
<tr>
<td>Bunsen solubility coefficient for $O_2$</td>
</tr>
<tr>
<td>in RBC, mmol·ml$^{-1}$·Hg$^{-1}$</td>
</tr>
<tr>
<td>Bunsen solubility coefficient for $O_2$</td>
</tr>
<tr>
<td>in plasma, mmol·ml$^{-1}$·Hg$^{-1}$</td>
</tr>
<tr>
<td>Bunsen solubility coefficient for $O_2$</td>
</tr>
<tr>
<td>in interstitium, mmol·ml$^{-1}$·Hg$^{-1}$</td>
</tr>
<tr>
<td>Half-saturation in Hill equation, mmHg</td>
</tr>
<tr>
<td>Hill equation parameter</td>
</tr>
<tr>
<td>Initial overall heme group concentration, mol/l</td>
</tr>
</tbody>
</table>
among of oxygen present in DVR blood at the corticomedullary junction is only \(4.0 \times 10^{-6}\) mmol/s, which is smaller than the oxygen consumption rate both in the OM and IM (\(4.0 \times 10^{-5}\) and \(6.7 \times 10^{-6}\) mmol/s, respectively). Even with a higher initial \(P_{O2}\) of 65 mmHg and an initial single vessel blood flow rate of 10 nl/min, the maximum supply is found to be \(4.6 \times 10^{-4}\) mmol/s. Moreover, because of the large permeability of vasa recta to oxygen, a large fraction of oxygen is transported radially from DVR to AVR in the OM, as shown below. Thus the net amount of oxygen reabsorbed from vasa recta into the medullary interstitium should be even lower than the estimate of \(4.6 \times 10^{-4}\) mmol/s calculated above.

We conclude that the amount of oxygen supplied by DVR is significantly smaller than the estimated oxygen consumption in the renal medulla. Given this discrepancy (reasons for which are discussed further below), the net amount of oxygen reabsorbed from vasa recta into the medullary interstitium is estimated based on independent data, as shown below. Values for all the other parameters needed to solve the transport equations for oxygen are listed in Table 2.

### RESULTS

Because many parameters related to oxygen transport remain unknown or uncertain, we performed several parametric studies to determine how variations in oxygen metabolic requirements, medullary blood flow rate, hematocrit, vasa recta permeability to oxygen, and initial \(P_{O2}\) affect oxygen transport and \(P_{O2}\) distribution in the medulla. As described above, it was not possible to relate the net amount of oxygen that is reabsorbed from vasa recta into the interstitium for consumption referred to hereafter as the consumption rate of DVR-supplied oxygen to the metabolic requirements of the renal medulla. We therefore began by estimating upper and lower limits for this consumption rate based on available measurements of \(P_{O2}\) at varying depths of the renal medullary interstitium.

#### Estimate of Net Amount of Oxygen Reabsorbed From Vasa Recta

As reviewed above, reported measurements suggest that the interstitial \(P_{O2}\) lies between 35 and 45 mmHg at the corticomedullary junction and between 10 and 20 mmHg at the papillary tip. The general form of the interstitial \(P_{O2}\) profile was taken as

\[
\text{Interstitial } P_{O2}(x) = ax^b + c \tag{31}
\]

where \(a\) and \(c\) were determined by interstitial \(P_{O2}\) values at \(x = 0\) and 1, respectively. Measurements by Brezis et al. (5) indicate that the average interstitial \(P_{O2}\) is \(\sim 30\) mmHg between 0 and 1 mm below the OM and 20 mmHg between 1 and 2 mm below that, albeit with very significant variations. Both to predict values in agreement with these data and to minimize the number of parameters, we fixed the value of \(b\) at 0.50.

To deduce the consumption rate of DVR-supplied oxygen (\(R_{O2}\)) from interstitial \(P_{O2}\) profiles, assumptions regarding the value of uncertain parameters need to be made. If \(P_{O2}\) is fixed in the interstitium, the oxygen consumption rate increases with increasing blood flow rate, hematocrit, and \(P_{O2}\) in DVR at the corticomedullary junction (hereafter referred to as initial DVR \(P_{O2}\)). It decreases with increasing vasa recta permeability to oxygen and \(P_{O2}\) in DVR at the papillary tip (results not shown). To determine an upper bound for \(R_{O2}\), we therefore assigned to those parameters that exhibit a positive correlation with \(R_{O2}\), their highest estimated values and to those that exhibit a negative correlation their lowest estimated values (and vice versa for the lower bound). We also determined the value of \(R_{O2}\) when intermediate, baseline values were chosen.

The results shown in Table 3 indicate that the overall consumption rate for DVR-supplied oxygen is on the order of \(10^{-6}\) mmol/s and is perhaps fivefold as high or one-fourth as low: our simulations yielded values of \(5.0 \times 10^{-6}\) and \(2.7 \times 10^{-7}\) mmol/s as the upper and lower limits for \(R_{O2}\), respectively. Hence, the baseline value for subsequent parametric studies was taken as \(1.0 \times 10^{-6}\) mmol/s.

In most physiological situations, metabolic requirements (i.e., oxygen consumption rate) determine \(P_{O2}\) in the interstitium and not vice versa. To investigate oxygen transport in the renal medulla, we therefore fixed \(R_{O2}\) rather than interstitial \(P_{O2}\) in the remainder of this study. Baseline parameter values are given in Table 4.

### Table 4. Baseline parameter values

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial DVR (P_{O2}) ((x = 0)), mmHg</td>
<td>55</td>
</tr>
<tr>
<td>(R_{O2}), mmol/s</td>
<td>(1.0 \times 10^{-6})</td>
</tr>
<tr>
<td>(P_{O2}), cm/s</td>
<td>0.01</td>
</tr>
<tr>
<td>(h_0)</td>
<td>3</td>
</tr>
<tr>
<td>(q_{b0}), nl/min</td>
<td>9</td>
</tr>
<tr>
<td>(H_0), %</td>
<td>25</td>
</tr>
</tbody>
</table>

\(h_0\), Wall-to-RBC permeability ratio; \(q_{b0}\), initial blood flow rate in a single vessel.
Effect of Spatial Distribution of Oxygen Consumption

Given the total consumption rate for oxygen supplied by DVR, the local, volumetric oxygen consumption rate needs to be specified. If most of the DVR-supplied oxygen serves for the active reabsorption of sodium along the pars recta of the PT and the mTAL, it is likely that volumetric consumption rates are higher in the OM than in the IM. However, if a significant portion of oxygen is provided by other sources, it is possible that the local consumption rate of DVR-supplied oxygen remains approximately constant in the medulla. To account for all these possibilities, we postulated the following spatial distribution for the local, volumetric consumption rate

\[ r_{O2}(x) = r_0 \exp[s(1 - x/L)] \]  

(32)

where \( L \) is the total length of the medulla and \( r_0 \) and \( s \) are constants to be determined. The parameter \( s \) is a scaleup factor; the higher the value of \( s \), the larger the axial gradient in \( r_{O2} \), that is, the larger the difference in volumetric consumption rates between the OM and IM. Conversely, if \( s \) equals zero, \( r_{O2} \) remains constant throughout the medulla. Once \( s \) is fixed, the parameter \( r_0 \) is determined given the overall consumption rate for \( (R_{O2}) \)

\[ R_{O2} = LN_{DVR}(x = 0) \int_0^1 \frac{r_{O2}(x) A_{int}(x)}{N_{DVR}(x)} \, dx \]  

(33)

where \( N_{DVR} \) is the number of DVR and \( A_{int} \) is the interstitial cross-sectional area. A similar derivation is given by Edwards et al. (11) for water, sodium, and urea.

It may be interesting to note that the three cases examined in Table 3 exhibited different profiles for the local \( r_{O2} \). In determining the upper limit for the overall consumption rate of DVR-supplied oxygen, \( r_{O2} \) was found to remain approximately constant. In the other two cases, it was seen to decrease exponentially along the corticomedullary axis. It is therefore difficult to make hypotheses regarding the spatial distribution of the volumetric oxygen consumption rate based on these results.

Shown in Fig. 2 is \( P_{O2} \) in DVR, AVR, and the interstitium along the corticomedullary axis, assuming that the local volumetric consumption rate is constant, i.e., \( s = 0 \). As blood flows down along DVR toward the papillary tip, oxygen frees itself from hemoglobin, diffuses across the capillary wall into the interstitium, and is either consumed for metabolic processes or diffuses back into AVR. The DVR-to-AVR \( P_{O2} \) difference at the corticomedullary junction is proportional to the net amount of oxygen reabsorbed from the microcirculation, that is, \( R_{O2} \).

Shown in Fig. 3 are interstitial \( P_{O2} \) profiles for values of \( s \) ranging between 0 and 3, with \( R_{O2} \) equal to \( 1.0 \times 10^{-6} \) mmol/s. As \( s \) increases, oxygen consumption increases near the corticomedullary junction but decreases near the papillary tip, and \( P_{O2} \) at the tip remains higher even though the total amount of oxygen reabsorbed from the microcirculation is kept constant. Indeed, at the corticomedullary junction, \( P_{O2} \) is fixed independently of \( s \) in both DVR and AVR, because \( R_{O2} \) is given; in addition, near the junction, oxygen consumption is relatively small compared with transcapillary fluxes from DVR. Therefore, small adjustments in interstitial \( P_{O2} \) suffice to satisfy changes in local oxygen consumption rates. Conversely, near the papillary tip, the local oxygen consumption rate is
twice as large as the radial oxygen fluxes from DVR and AVR, both of which supply oxygen to the interstitium in this region. Moreover, plasma oxygen levels far from the corticomedullary junction are determined by accumulated changes in the local consumption rate; hence the significant variations in PO2 with s at the papillary tip.

If $R_O$ is set to $1.5 \times 10^{-6}$ mmol/s, convergence cannot be reached with values of s lower than 2. Indeed, for small values of s, volumetric oxygen consumption rates near the papillary tip are significantly high; due to radial diffusion of oxygen across vasa recta throughout the medulla, there is not enough oxygen in the lower regions to satisfy those large requirements, and hence the absence of convergence. With s equal to 2, however, the interstitial PO2 at the papillary tip is found to be 14 mmHg, a value that agrees well with experimental observations (see above).

**Effect of Total Oxygen Consumption Rate**

By infusing furosemide, which inhibits reabsorption of sodium at TALs, into blood, Brezis et al. (3) reported an increase in medullary PO2 from 16 ± 4 to 35 ± 4 mmHg without changes in cortical PO2. The theoretical effects of changes in oxygen metabolic requirements were simulated using our model. Figure 4 shows the effect of varying the consumption rate of DVR-supplied oxygen on PO2 at the papillary tip for two values of s, 0 and 2. As expected, lower oxygen consumption rates resulted in higher medullary PO2. If oxygen supply is sufficient, PO2 at the tip decreases linearly with the increase in total oxygen consumption rate. Beyond a certain $R_O$ value ($1.2 \times 10^{-6}$ and $1.5 \times 10^{-6}$ mmol/s for s = 0 and 2, respectively), however, the amount of oxygen still present in blood becomes critical near the papillary tip, so that a little increase in oxygen consumption leads to a sharp drop in PO2, and with further increases in $R_O$, simulations fail to converge.

These limiting values are well below the upper limit for $R_O$ that we calculated initially, i.e., $5.0 \times 10^{-6}$ mmol/s. This stems from the fact that all parameters were optimized to obtain this upper estimate, whereas they are assigned their baseline values in Fig. 4.

**Effect of Initial PO2 in DVR**

Very little change in medullary PO2 has been observed experimentally in response to increased arterial PO2 up to 650 mmHg (15). This finding was confirmed by our results. Changes in PO2 at the corticomedullary junction in DVR do not affect PO2 at the papillary tip very significantly, as illustrated in Fig. 5. Because a significant portion of oxygen is transported radially from DVR to AVR near the corticomedullary junction, a 20-mmHg increase in initial PO2 has little effect on PO2 at the papillary tip (the latter increases from 22.1 to 23.7 mmHg only with s = 2 and from 17.0 to 19.0 mmHg with s = 0). That is, radial diffusion (or oxygen shunting) tends to eliminate the downstream effects of systemic blood pressure changes.

**Effect of Oxygen Transport Resistance Distribution**

As described above, intraluminal oxygen transport resistance comes from the RBC membrane and its adjacent boundary layer (RBC resistance) and from the capillary wall and its boundary layer in plasma (wall resistance). On the basis of the study by Hellums et al. (18), we estimated that the wall-to-RBC oxygen permeability ratio ($h_r$) is equal to 3 (see above). However, the value of this parameter remains highly uncertain. Shown in Fig. 6 is the interstitial PO2 at the papillary tip as a function of $h_r$ for a given total capillary permeability to oxygen equal to 0.01 cm/s.
The higher hr, the higher the wall permeability to oxygen; thus the higher the transcapillary oxygen fluxes between DVR and AVR and the lower the PO2 at the papillary tip. Overall, however, hr has a small effect on PO2. A fivefold increase in hr only reduced PO2 at the tip by \(\frac{1}{10}\) mmHg. Our baseline value of 3 therefore seems reasonable.

**Effect of Capillary Permeability to Oxygen**

As reviewed above, estimates for the capillary permeability to oxygen range between 0.027 and 0.035 cm/s in the study by Hellums et al. (18) and between 0.05 and 0.13 cm/s in that by Eggleton et al. (14). Experimental values of vasa recta wall permeability to sodium, on the order of \(10^{-3}\) cm/s, can only provide a rough lower bound estimate for \(P_{O_2}^C\), because oxygen is a gaseous and neutral molecule compared with sodium. The permeability of DVR and AVR to oxygen was therefore varied between 0.001 and 0.1 cm/s, with a baseline value of 0.01 cm/s. Because the endothelium of AVR is fenestrated, whereas that of DVR is continuous, ascending vessels are expected to be more permeable to oxygen than descending ones. We first assumed that \(P_{O_2}^C\) in DVR was identical to that in AVR, and we then varied their ratio.

Illustrated in Fig. 7 are the effects of changes in vasa recta permeability to oxygen on interstitial PO2 profiles; the total oxygen consumption rate was fixed at \(1.0 \times 10^{-6}\) mmol/s and two values of s were examined, 0 and 2. With a permeability of 0.001 cm/s, transcapillary oxygen transport is so low that the corticomedullary (i.e., axial) oxygen gradient is close to zero. As capillary permeability increases, more oxygen is transferred radially across vasa recta and the interstitium, thereby augmenting the corticomedullary oxygen gradient. Simulations fail to converge for permeability values higher than 0.012 cm/s for \(s = 0\) (and 0.016 cm/s for \(s = 2\)) because oxygen levels drop to zero before blood reaches the papillary tip. These upper estimates are lower than the ranges from the studies by Hellums et al. (18) and Eggleton et al. (14), but the latter were not specific to renal medullary vasa recta. Comparison between the predicted interstitial PO2 profile and experimental findings (see above) suggest that vasa recta permeability to oxygen is on the order of 0.01 cm/s.

We then varied the ratio of \(P_{O_2}^C\) in AVR to that in DVR. The results, shown in part in Table 5, indicate that increasing the relative permeability of AVR to oxygen only has a small effect on interstitial PO2, even when the wall-to-RBC permeability ratio is as low as 1. As expected, the higher the permeability of AVR, the greater the radial shunting of oxygen and the lower the PO2 at the papillary tip; however, increasing AVR permeability by a factor 10 reduces PO2 by \(<1\) mmHg. Assuming that DVR and AVR have an identical permeability to oxygen, therefore, appears reasonable.

**Fig. 6.** Effect of the wall-to-red blood cell (RBC) oxygen permeability ratio on interstitial PO2 at the papillary tip for \(s = 0\) and 2.

**Fig. 7.** Effect of capillary permeability to oxygen on interstitial PO2 profiles. A: \(s = 0\); B: \(s = 2\). The permeability is taken to be identical in DVR and AVR.
Effect of Blood Flow

Investigators have reported decreases in cortical PO₂ combined with increases in medullary PO₂ after renal hypoperfusion by hemorrhage, aortic tie, or nitroprusside infusion (6). Whereas hypoperfusion can decrease the glomerular filtration rate and hence oxygen consumption due to the parallel decrease in active reabsorption, it can also induce dilation of vasa recta, leading to an increase in medullary blood flow. We therefore examined the effects of variations in blood flow rate on medullary PO₂. The reported range for the initial DVR blood flow rate in a single vessel (q₀) is in fact relatively large, from 8 to 10 nl/min (27).

Illustrated on Fig. 8 is the effect of blood flow rate on interstitial PO₂ at the papillary tip, with a constant overall consumption rate of 1.0 × 10⁻⁶ mmol/s. As expected, PO₂ at the papillary tip decreases with decreasing blood flow rate at the corticomedullary junction as oxygen supply is reduced. Below q₀ values of 8–9 nl/min, depending on the value of s (i.e., on the spatial distribution of oxygen consumption), PO₂ at the papillary tip falls sharply because the amount of available oxygen reaches critically low values.

Effect of Hematocrit

Addition of RBCs to the perfusion fluid in isolated rat kidney studies considerably reduces hypoxic damage to mTALs (15, 33). Simulations in which we varied the initial hematocrit (H₀) confirmed experimental findings.

The H₀ is set at 0.25 in our baseline case (27), a value far lower than that in most other vessels, in which the hematocrit is between 0.4 and 0.5. In the renal medulla, however, a value as low as 0.086 was reported by Rasmussen (28). Possible reasons for low renal medullary blood hematocrit include plasma skimming in juxtamedullary afferent arteries, Fahraeus effects, and RBC shrinkage (27).

As illustrated in Fig. 9, variations in H₀ significantly affect PO₂ profiles. Increasing the H₀ from 25% to 50% raises papillary tip PO₂ from 23.5 to 35.2 mmHg in our baseline case, due to increased binding to hemoglobin in RBCs and thus reduced oxygen shunting between plasma DVR and AVR. If RO₂ is maintained at 1.0 × 10⁻⁶ mmol/s, H₀ needs to be >0.17 to avoid oxygen depletion in the IM.

Similarly, decreasing the concentration of hemoglobin within erythrocytes sharply reduces PO₂ at the papillary tip (results not shown), because hemoglobin acts as a reservoir for oxygen. Binding of oxygen to hemoglobin thus plays an important role in modulating radial transport of oxygen and preventing hypoxia. In the absence of RBCs, the baseline oxygen consumption rate cannot be sustained. Even without any consumption of oxygen, if the hemoglobin concentration is maintained at 5.1 mmol/cm³, the H₀ must be >0.1% to maintain PO₂ at the papillary tip close to 15 mmHg.

Those results confirm reports by Alcorn et al. (1) and Endre et al. (15), who found that erythrocyte-free perfusion of the isolated perfused kidney results in segmental necrosis of the nephron in the OM.

Table 5. Effect of variations in AVR-to-DVR oxygen permeability ratio on interstitial PO₂ at the papillary tip

<table>
<thead>
<tr>
<th>fₓD</th>
<th>fₓA</th>
<th>fₓB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.8</td>
<td>25.1</td>
</tr>
<tr>
<td>5</td>
<td>23.3</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Values of PO₂ at the papillary tip are given in mmHg. fₓD, AVR-to-DVR oxygen permeability ratio; that is, PO₂(W) (AVR)/PO₂(W) (DVR), where PO₂(W) is the permeability of the plasma-capillary wall interface to oxygen. The capillary permeability of DVR to oxygen is fixed at 0.01 cm/s.

Fig. 9. Effect of initial hematocrit on interstitial PO₂ at the papillary tip for s = 0 and 2.
OXYGEN TRANSPORT IN THE RENAL MEDULLA

Table 6. Effect of variations in critical parameters on interstitial PO2 at the papillary tip

<table>
<thead>
<tr>
<th>Fixed Parameters</th>
<th>Interstitial PO2 (x = 1), mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfc, cm/s</td>
<td>RO2, mmol/s</td>
</tr>
<tr>
<td>0.0160</td>
<td>1.0 × 10^{-6}</td>
</tr>
<tr>
<td>0.0165</td>
<td>1.0 × 10^{-6}</td>
</tr>
<tr>
<td>0.01</td>
<td>1.55 × 10^{-6}</td>
</tr>
<tr>
<td>0.01</td>
<td>1.60 × 10^{-6}</td>
</tr>
<tr>
<td>0.01</td>
<td>1.0 × 10^{-6}</td>
</tr>
<tr>
<td>0.01</td>
<td>1.0 × 10^{-6}</td>
</tr>
<tr>
<td>0.01</td>
<td>1.0 × 10^{-6}</td>
</tr>
<tr>
<td>0.01</td>
<td>1.0 × 10^{-6}</td>
</tr>
</tbody>
</table>

For Pfc and RO2, three significant digits are needed to show that small variations in parameter values significantly affect medullary PO2.

DISCUSSION

Our model accounts only for those DVR and AVR that form vascular bundles in the OM and are destined to the IM. The total amount of oxygen carried by blood flowing along those vasa recta is significantly lower than estimated metabolic oxygen requirements in the renal medulla, in particular for active sodium reabsorption along PTs and mTALs. Nevertheless, based on reported measurements of interstitial PO2 in the medulla, we estimated that lower and upper limits for the consumption rate of oxygen supplied by DVR blood flow are 2.7 × 10^{-7} and 5.0 × 10^{-6} mmol/s, respectively.

Setting RO2 within this range, we then explored the relationships among oxygen consumption rate, medullary PO2, capillary permeability to oxygen, and initial conditions in DVR at the corticomedullary junction, such as PO2, blood flow rate, and hematocrit.

Our predictions were in agreement with a number of experimental findings. Both this study and that of Endre et al. (15) indicate that initial PO2 at the corticomedullary junction in DVR (or arterial PO2) only has a small effect on interstitial PO2 profiles. We found that with baseline parameters, a 20-mmHg change in initial PO2 results in a drop of papillary tip PO2 smaller than 2 mmHg, due to oxygen shunting between DVR and AVR (i.e., radial transport across the medullary interstitium). In accordance with the experimental observations of Schurek and Kriz (33) and Endre et al. (15), our simulations show that augmenting the hematocrit increases the oxygen reservoir and reduces diffusional shunting by increasing binding to hemoglobin, and therefore leads to higher PO2 levels at the papillary tip. Similar effects are seen when the hemoglobin concentration within RBCs is raised. In the absence of erythrocytes, it is not possible to maintain PO2 at the papillary tip above 10 mmHg, even when oxygen consumption is set to zero, due to the rapid diffusion of oxygen between DVR and AVR.

Our results also suggest that oxygen consumption rate, capillary permeability to oxygen, and initial blood flow rate significantly affect PO2 profiles. Increasing permeability to oxygen decreases PO2 at the papillary tip due to facilitated radial diffusion of oxygen from DVR to AVR, that is, increased shunting. Increasing RO2 or decreasing the blood flow rate results in lower PO2 values at the papillary tip, as expected, because less oxygen reaches the lower medullary regions in both cases.

Reported measurements suggest that interstitial PO2 at the papillary tip lies between 4 and 20 mmHg. Our results indicate that if it is <20 mmHg, irrespective of the values of capillary permeability to oxygen, oxygen consumption rate, initial blood flow rate, and H0, a small increase in the first two parameters or a small decrease in the last two leads to a sharp decrease in PO2 at the tip, as shown in Table 6, or even to the absence of convergence in our simulations, because oxygen has been depleted deep in the medulla. This suggests that the balance between oxygen supply and demand is critical because a small change in either may lead to hypoxia.

In addition, variations in the spatial distribution of the local, volumetric interstitial oxygen consumption rate significantly alter interstitial PO2 values in the IM. The greater the axial gradient in volumetric oxygen consumption rate, the higher PO2 levels near the papillary tip and the lower the risk of hypoxic injury. Because active sodium reabsorption occurs in PTs and mTALs, which are situated in the cortex and the OM, it is likely that oxygen requirements decrease along the corticomedullary axis, thereby limiting potential inner medullary damage due to oxygen shunting.

Our model of oxygen transport is limited in part by the fact that we do not account for the effect of local factors such as pH, CO2, and nitric oxide concentrations on the affinity of hemoglobin and oxygen (35). However, simulations in which we varied the relative association and dissociation rates of Hb and O2 instead of assuming equilibrium (i.e., instead of using the Hill equation) suggest that changes in reaction kinetics may not highly affect our results. Assuming that the dissociation rate is 10 times lower than the reported value found in Clark et al. (9), PO2 at the papillary tip increases by <4%, as shown in Table 7. As the dissociation rate further decreases, the amount of oxygen that is free to diffuse radially between the vessels is increasingly reduced and PO2 at the papillary tip increases more significantly.

Given the uncertainty in several parameters of the model, we searched for a combination of values that would yield PO2 values at the papillary tip between 10 and 20 mmHg, in the range of most reported measure-
ments. Assuming that the capillary permeability to oxygen is equal to 0.01 cm/s and that the volumetric oxygen consumption rate decreases exponentially (with \( s = 2 \) in Eq. 32), we found that an overall DVR-supplied oxygen consumption rate of \( 1.5 \times 10^{-6} \) mmol/s yields a papillary tip \( \text{PO}_2 \) equal to 14 mmHg.

This \( \text{RO}_2 \) value is more than 10 times lower than the estimated amount of oxygen consumed by active sodium reabsorption solely along mTALs, \( 1.7 \times 10^{-5} \) mmol/s. This discrepancy indicates that there are other significant sources of oxygen in the renal medulla, and/or that tissue oxygen requirements are lower than estimated. These two hypotheses are examined in turn below.

Our estimate of oxygen in DVR blood flow is based on those vessels that are destined toward the IM. Some blood goes to the capillary plexus, which feeds the interbundle region and is not accounted for in our model; nevertheless, this fraction of medullary blood flow is expected to be small. The amount of oxygen that is delivered from the cortex to the medulla by dissolution in the tubular fluid should be equally small. Over 95% of the oxygen carried by blood is within RBCs, so that the amount of oxygen in the erythrocyte-free filtrate must therefore be low. It has also been suggested that diffusion of oxygen may occur via a nonvascular pathway, which might explain why the cortex wraps itself around the pelvis and the medulla (T. L. Pallone, personal communication). Finally, Ulfendahl (34) and Leonhardt et al. (20, 21) found that \( \text{PO}_2 \) is slightly higher in urine than at the papillary tip or a little above. It is therefore possible that some oxygen is transported from the ureter across the pelvic epithelium near the papillary tip; this local supply, however, would not explain the discrepancy in the rest of the medulla.

It is equally likely that the estimate of medullary oxygen consumption that we derived is too elevated. Studies designed to correlate oxygen requirements with transport work in various nephron parts are based on isolated segments and maximal transport rates and do not account for oxygen shunting in the intact kidney; they may yield significant overestimates of oxygen consumption as a consequence. In vivo, furosemide, a loop diuretic that blocks active reabsorption of NaCl in the TAL, has been shown to increase medullary \( \text{PO}_2 \) from 16 ± 4 to 35 ± 5 mmHg (3). The results illustrated in Fig. 4 suggest that the corresponding reduction in the oxygen consumption rate is \( \sim 1 \times 10^{-6} \) mmol/s with baseline parameters, that is, an order of magnitude less than estimated oxygen requirements for mTALs. The possibility that anaerobic metabolism is a nonnegligible source of energy in the medulla must be considered as well. The mTAL, and the S3 segment of the PT to a lesser extent, can generate ATP by glycolysis when oxidative metabolism is impaired (22). Schurek and Johns (31) have proposed that the limited oxygen supply to the nephron forces TAL segments to oscillate between aerobic and anaerobic energy production. Brezis and Epstein (4) have also suggested that self-regulation of mitochondrial respiration may occur in hypoxia, with enzymes such as aconitase and cytochrome playing a key role in profoundly reducing metabolic activity. In well-oxygenated tissues, cytochrome \( a,a_3 \) is almost completely oxidized because of its high affinity for oxygen. In rat kidneys, Epstein et al. (16) have shown that 25–40% of cytochrome \( a,a_3 \) is in its reduced form and that a decrease in medullary transport induced by loop diuretics produces an increase in oxidation. mTALs thus appear to be an important site of reduced cytochrome oxidase, and mTAL cells may normally operate on the brink of anoxia, carrying out significant transport functions even when they are not fully saturated with oxygen.

In summary, our model suggests that the net amount of oxygen reabsorbed from vasa recta into the medullary interstitium is on the order of \( 10^{-6} \) mmol/s and capillary permeability to oxygen \( \sim 0.01 \) cm/s. Medullary hypoxia results from radial shunting of oxygen between DVR and AVR and is reduced by higher blood flow and increased hemocrit, as well as decreased tubular sodium reabsorption. Small variations in any of these three variables can lead to drastic changes in papillary tip \( \text{PO}_2 \).

**APPENDIX A**

**Expression for the Cell-to-Wall Surface Area Ratio in a Multiunit Model**

An expression for the cell-to-wall surface area ratio (\( \Gamma \)) when a single DVR is considered was obtained by Pallone et al. (26). We extended their calculation to account for the fact that the number of vasa recta changes along the corticomedullary axis.

For a volume element of length \( x \) in a single vessel, the average number of RBCs is

\[
N_{\text{RBC}} = \frac{A_D x}{v} \left( \frac{q^R}{q^W} + \frac{q^W}{q^R} \right) = \frac{A_D x}{v} \left( \frac{Q^R}{Q^W} + \frac{Q^W}{Q^R} \right)
\]

where \( v \) is the volume of a single RBC; \( A \) is the cross-sectional area of the vessel, \( q^R \) and \( q^W \) are the volume flow rates in RBCs and plasma in a single vessel, respectively; and \( Q^R \) and \( Q^W \) are the corresponding values for all vasa recta.

Conservation of the number of RBCs in a single DVR yields

\[
\frac{Q^R}{N_v} = \frac{Q^R_0}{N_0 N_v}
\]

where \( N \) is the number of vasa recta and the subscript 0 corresponds to values in DVR at the corticomedullary junction. The ratio of the surface area of RBCs to that of vasa recta walls in DVR (\( \Gamma_{\text{DVR}} \)) is defined as

\[
\Gamma_{\text{DVR}} = \frac{s N_{\text{RBC}}}{\pi D_A x}
\]

where \( s \) is the surface area of a RBC and \( D \) is the diameter of a vessel. Substituting Eq. A1 into Eq. A3 and replacing \( A \) with \( HD^3/4 \), we obtain

\[
\Gamma_{\text{DVR}} = \frac{s D}{4v} \left( \frac{Q^R}{Q^W} + \frac{Q^W}{Q^R} \right)
\]
and 8.16 μm, respectively. As RBCs swell or shrink, \( Q^R \) and \( v \) vary along the corticomedullary axis. If we assume that RBCs expand or contract only in the radial direction and if we neglect the surface area at both ends of the cylinder, we have

\[
\frac{s_0}{s} \cdot \frac{D}{D} = \frac{v_0^{0.5}}{v} = \left( \frac{Q^R_N}{Q^R N_0} \right)^{0.5} \tag{A5}
\]

Substituting Eqs. A2 and A5 into Eq. A4 yields

\[
\Gamma_{DVR} = \left( \frac{s_0D}{4v_0} \right) \left( \frac{Q^R_N}{Q^R N_0} \right)^{0.5} \tag{A6}
\]

Given that one DVR gives rise to \( N_v \) AVR, a similar reasoning yields the following expression for the cell-to-wall surface area ratio in AVR

\[
\Gamma_{AVR} = \left( \frac{s_0D}{4v_0} \right) \left( \frac{Q^R_N}{Q^R N_0} \right)^{0.5} \tag{A7}
\]

**APPENDIX B**

**Derivation of Eq. 22 for Oxygen Conservation in RBCs**

Equation 22, which serves to eliminate the unknown oxyhemoglobin dissociation rate \( R \) from oxygen conservation equations, is derived as follows. Equation 21 can be rewritten as

\[
\frac{C^{R}_{\text{HbO}_2}}{C^{R}_{\text{Hb}}} = \left( \frac{C^{R}_{\text{HbO}_2}}{C^{R}_{\text{Hb}}} \right)^a \tag{B1}
\]

Taking the derivative of Eq. B1, we obtain

\[
d\frac{C^{R}_{\text{HbO}_2}}{dx} = \frac{dC^{R}_{\text{Hb}}}{dx} + n\frac{C^{R}_{\text{Hb}}}{C^{R}_{\text{Hb}}} \frac{dC^{R}_{\text{O}_2}}{dx} \tag{B2}
\]

Adding Eqs. 19 and 20 yields, after rearrangement

\[
d\frac{C^{R}_{\text{Hb}}}{dx} = \frac{1}{q^R} \left[ q^R \frac{dC^{R}_{\text{O}_2}}{dx} + C^{R}_{\text{Hb}} n \frac{dC^{R}_{\text{O}_2}}{dx} \right] = 0 \tag{B3}
\]

By substituting Eq. B3 into Eq. B2 to eliminate the \( dC^{R}_{\text{Hb}}/dx \) term and rearranging the resulting expression, we obtain

\[
\left( 1 + \frac{C^{R}_{\text{HbO}_2}}{C^{R}_{\text{Hb}}} \right) \frac{dC^{R}_{\text{HbO}_2}}{dx} = \frac{q^R n C^{R}_{\text{Hb}}}{C^{R}_{\text{Hb}}} \left( \frac{C^{R}_{\text{HbO}_2}}{C^{R}_{\text{Hb}}} \right)^a \frac{dC^{R}_{\text{O}_2}}{dx} \tag{B4}
\]

A comparison between Eqs. B4 and 20 shows that

\[
R = - \frac{C^{R}_{\text{HbO}_2}}{C^{R}_{\text{Hb}}} \left( \frac{q^R n C^{R}_{\text{Hb}}}{C^{R}_{\text{Hb}}} \right) \frac{dC^{R}_{\text{O}_2}}{dx} \tag{B5}
\]

By substituting this expression for \( R \) in Eq. 18 we obtain

\[
d\frac{C^{R}_{\text{O}_2}}{dx} = \frac{q^R}{C^{R}_{\text{O}_2}} \left[ 1 + \frac{n}{C^{R}_{\text{O}_2}} \left( \frac{C^{R}_{\text{HbO}_2}}{C^{R}_{\text{Hb}}} \right) \right] = -J_0^{R} \frac{\Gamma_{DVR}}{\pi D} \tag{B6}
\]

The Hill equation can be employed to eliminate the two remaining unknown concentrations \( C^{R}_{\text{HbO}_2} \) and \( C^{R}_{\text{Hb}} \) in Eq. B6. Rearranging Eq. 21, we obtain

\[
C^{R}_{\text{HbO}_2} = \frac{\left( C^{R}_{\text{O}_2}/C^{R}_{\text{O}_2} \right)^a}{1 + \left( C^{R}_{\text{O}_2}/C^{R}_{\text{O}_2} \right)^a} \left( C^{R}_{\text{HbO}_2} + C^{R}_{\text{Hb}} \right) \tag{B7}
\]

\[
C^{R}_{\text{Hb}} = \frac{\left( C^{R}_{\text{HbO}_2} + C^{R}_{\text{Hb}} \right)}{1 + \left( C^{R}_{\text{HbO}_2}/C^{R}_{\text{O}_2} \right)^a} \tag{B8}
\]

Finally, by substituting Eqs. B7 and B8 into Eq. B6, we obtain the expression corresponding to Eq. 22 in the text

\[
C^{R}_{\text{O}_2} \frac{dq^R}{dx} + q^R \frac{dC^{R}_{\text{O}_2}}{dx} \left[ 1 + \frac{n}{C^{R}_{\text{O}_2}} \left( \frac{C^{R}_{\text{HbO}_2}/C^{R}_{\text{Hb}}} \right) \right] = -J_0^{R} \frac{\Gamma_{DVR}}{\pi D} \quad (B9)
\]

We thank Dr. Thomas Pallone for helpful discussions. This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-53775.

**REFERENCES**