Interstitial water and solute recovery by inner medullary vasa recta

AURÉLIE EDWARDS,1 MARK J. DELONG,2 AND THOMAS L. PALLONE3

1Department of Chemical Engineering, Tufts University, Medford, Massachusetts 02155; 2Department of Chemical Engineering, Pennsylvania State University, University Park, Pennsylvania 16802; and 3Division of Nephrology, University of Maryland School of Medicine, Baltimore, Maryland 21201

The microcirculation in the renal medulla must remove solutes and water recovered from nephrons while preserving the corticomedullary gradients of sodium and urea generated by the loops of Henle and collecting tubules. This dual task is made possible by the countercurrent arrangement of the vasa recta. Descending vasa recta (DVR) arise from the efferent arterioles of juxtamedullary glomeruli, travel through the outer medulla, and diverge at varying levels to be converted into ascending vasa recta (AVR), which then return to the cortex. The structural properties of DVR and AVR differ considerably. DVR have continuous endothelial cells and intercellular tight junctions, whereas AVR have a highly fenestrated endothelium.

The precise role of the renal medullary microcirculation in regulating water and solute excretion remains to be elucidated. Models of the urinary concentrating mechanism have generally neglected the role of vasa recta by assuming that the capillaries offer negligible resistance to transport of solute and water (13, 30). However, anatomical differences between the outer and inner medulla, ultrastructural heterogeneities between DVR and AVR, and the existence of facilitated transport pathways in DVR suggest that the microvasculature plays a significant role in the trafficking of sodium and urea. We therefore recently developed a multicompartment model of water and solute exchange between vasa recta and the interstitium (7). Both across DVR and AVR, the paracellular pathway is shared by water and solutes, and transport is driven by hydraulic and oncotic pressure differences across the walls (classic Starling forces). In addition, two transcellular pathways are present in DVR: aquaporin-1 water channels (AQP1), which are impermeable to all solutes, and urea transporters, the presence of which raises DVR permeability to urea by a factor of 4 (24).

Water, sodium, and urea are reabsorbed into the interstitium from the limbs of Henle’s loop and the collecting ducts. These inputs were not accounted explicitly in our previous approach. Instead, exponential increases in urea and sodium concentrations were specified in the inner medulla based on electron microscope data obtained by Koepsell et al. (11), and the fractional osmolality due to sodium was determined by interpolating the data of Atherton et al. (1). Wang and co-workers (36, 37) recently developed a simple but elegant analytic model of microvascular exchange, in which a countercurrent capillary loop is embedded in a secretory epithelium. Their latest predictions show good agreement with the experimental data of Koepsell et al. (11), but their theoretical approach is constrained by the need for analytic, closed solutions. Wang and Michel (37) do not account for the exchange of fluid and macromolecules, thereby neglecting significant coupling between the transport of water, small solutes, and proteins. Moreover, they specify a constant solute input...
rate into the interstitium per unit axial length. Little is known about where and how much fluid and small solutes are reabsorbed from the loops of Henle and the collecting ducts. To determine how the spatial distribution of interstitial water and solutes affects concentration profiles and the axial osmolality gradient in the inner medulla, we extended our previous multiunit model to account explicitly for water and solute input rates in the medullary interstitium.

METHODS

Microvascular transport is simulated in the entire medulla. However, as described in Edwards and Pallone (7), we only consider vasa recta that are destined to the inner medulla. As a consequence, the number of DVR and AVR in the outer medulla is taken to be constant. In addition, since water and solute exchanges can only occur among DVR, AVR and the interstitium in the outer medullary vascular bundles, input rates are zero in the outer medulla.

Conservation equations. Mass balance and flux equations are described in detail in previous studies (6, 7) and briefly summarized below. If \( x \) is the axial coordinate, the total plasma flow rate, \( Q_P \), obeys the following conservation equation at steady state

\[
\frac{dQ_P}{dx} = \left[ \frac{J_P}{N} \right] \pi D + \left( \frac{Q_P}{N} \right) \frac{dN}{dx}
\]

where “+” and “−” apply to AVR and DVR, respectively. The volume fluxes per unit membrane area (in cm/s) across the capillary wall and the red blood cell (RBC) membrane are denoted by \( J_P \) and \( J_{i} \), respectively. \( I \) is the ratio of cell-to-vessel surface area averaged over time, \( N \) is the number of vessels, and \( D \) is the vessel diameter. Mass balances for solutes to which RBCs are impermeable, such as sodium, albumin, and other plasma proteins, can be written as

\[
\frac{dQ_P C_i}{dx} = \left[ \frac{J_P C_i}{N} \right] \pi D + \left( \frac{Q_P}{N} \right) C_i \frac{dN}{dx}
\]

where \( C_i \) is the molar plasma concentration of solute \( i \) and \( J_i \) its molar flux per unit membrane area (in mmol·cm⁻²·s⁻¹) from plasma to interstitium. Conservation of urea, which is also exchanged across the RBC membrane, yields

\[
\frac{dQ_P C_u}{dx} = \left[ \frac{J_P C_u}{N} \right] \pi D + \left( \frac{Q_P}{N} \right) C_u \frac{dN}{dx}
\]

where \( J_P \) and \( J_{uc} \) are the paracellular and carrier-mediated transcapillary molar fluxes of urea, respectively, and \( J_{uc} \) is the molar flux of urea across RBCs.

The paracellular and transcellular volume fluxes (\( J_{vp} \) and \( J_{uc} \), respectively) from plasma to interstitium are given by

\[
J_{vp} = L_p(\Delta P - \sigma_a \Delta \Pi_w - \Delta \Pi_{pr})
\]

\[
J_{uc} = L_i[\Delta P - \Delta \Pi_w - \Delta \Pi_{pr} - RT \sum_{i=\text{sodium, urea}} \gamma_i (C_i - C)]
\]

where \( L_p \) and \( L_i \) represent the hydraulic conductivities of the paracellular and transcellular pathways, respectively, \( \Delta P \) is the transcapillary hydraulic pressure difference, \( \Delta \Pi_w \) and \( \Delta \Pi_{pr} \) are the transcapillary oncotic pressure differences due to albumin and other plasma proteins, respectively, and \( \sigma_a \) is the reflection coefficient of the paracellular pathway to albumin. The interstitial concentration of solute \( i \) (\( i = \text{albumin, sodium, urea} \)) across vasa recta walls is given by

\[
J_{uc} = L_p(\Delta P - \sigma_a \Delta \Pi_w - \Delta \Pi_{pr})
\]

\[
Pe = \left[ \frac{J_{uc}(1 - \sigma_a)}{P_i} \right]
\]

where \( P_i \) and \( \sigma_i \) are the (paracellular) permeability and reflection coefficient of the capillary wall to solute \( i \), respectively, and \( Pe \) is the Peclet number. Across the paracellular pathway, small solute reflection coefficients are taken to be zero. The transcapillary carrier-mediated flux of urea can be written as

\[
J_{uc} = P_{uc}(C_u - C_s)
\]

where \( P_{uc} \) is the permeability of urea transporters. Expressions for RBC fluxes are given in Edwards and Pallone (6).

Concentration polarization. In a previous study (7), we examined the assumption that the accumulation of protein in the interstitium at the walls of AVR may eliminate oncotic pressure differences across the AVR barrier. In that case, instead of Eq. 4, the expression for the AVR transmural volume flux becomes

\[
J_{vp}(AVR) = J_{vp}(AVR) - L_{pa} \Delta P - L_{pa} (P^A - P^I)
\]

where \( L_{pa} \) is the (paracellular) hydraulic conductivity of AVR, \( P^A \) denotes the hydraulic pressure in the AVR lumen, and \( P^I \) the hydraulic pressure in the interstitium (Since there are no AQP1 water channels in AVR, there is no transcellular component in the volume flux). This hypothesis leads to occasional inconsistencies. In some simulations, \( P^I \) remains very close to \( P^A \) throughout a large part of the medulla, meaning that little reabsorption or filtration occurs there, but concentration polarization must then be negligible, and that oncotic pressure differences should be accounted for.

In this work, we have adopted the intermediate approach of assuming that nonalbumin plasma proteins, but not albumin, exert oncotic pressure across the AVR wall. This is justified because the dominant protein available to be polarized in the interstitium is likely to be albumin and not larger globulins to which vessel walls are less permeable. With this approach, significant volume uptake occurs throughout the medulla, as observed experimentally (28), and transmural volume flux across AVR can be written as

\[
J_{vp}(AVR) = L_{pa} (\Delta P - \Delta \Pi_{pr})
\]

Interstitial hydraulic pressure and small solute concentration. The loops of Henle and collecting ducts across which water, sodium, and urea are exchanged with the interstitium lie in parallel with the vasa recta. Input rates are thus given per unit axial length per unit cross-sectional area of the interstitium. At any location along the corticomedullary axis, the sum of the fluxes from DVR and AVR, weighted according to their respective surface areas, must be equal and opposite
to the rate of generation in the interstitium

\[
\begin{align*}
\{ L_{\text{vp}}(x) + J_{\text{vp}}(x)N(x) + \pi D_{\text{DVR}}(x) \} + \{ L_{\text{Na}}(x)N(x) + \pi D_{\text{DVR}}(x) \} & + A_{\text{im}}(x)\psi_{\text{vp}}(x) = 0 \\
\{ L_{\text{Na}}(x)N(x) + \pi D_{\text{DVR}}(x) \} + \{ L_{\text{Na}}(x)N(x) + \pi D_{\text{DVR}}(x) \} & + A_{\text{im}}(x)\psi_{\text{Na}}(x) = 0 \\
\{ L_{\text{vp}}(x) + J_{\text{vp}}(x)N(x) + \pi D_{\text{DVR}}(x) \} + \{ L_{\text{vp}}(x)N(x) + \pi D_{\text{DVR}}(x) \} & + A_{\text{im}}(x)\psi_{\text{vp}}(x) = 0
\end{align*}
\]

where \( A_{\text{im}} \) is the cross-sectional area of the medullary interstitium (in cm²), and \( \psi_{\text{vp}}, \psi_{\text{Na}}, \text{and} \psi_{\text{vp}} \) are the local generation rates of volume, sodium, and urea, respectively, per unit area of interstitium. The latter three terms are taken to be zero in the outer medulla, where in the vascular bundles the exchange of water, sodium, and urea can only occur between vasa recta and interstitium. At a given depth \( x \), Eqs. 10a–10c when solved simultaneously yield the interstitial hydraulic pressure (\( P(x) \)) as well as sodium and urea interstitial concentrations.

The cross-sectional area of the inner medullary interstitium was calculated based upon that of the inner medulla, \( A_{\text{im}} \). The latter was determined by Becker (2) and can be approximated by the following polynomial

\[
A_{\text{im}}(x_{\text{im}}) = 0.175 - 0.3883(x_{\text{im}}/L_{\text{im}}) + 0.2606(x_{\text{im}}/L_{\text{im}})^2 - 0.04193(x_{\text{im}}/L_{\text{im}})^3
\]

where \( x_{\text{im}} \) is the dimensional coordinate along the corticomedullary axis in the inner medulla, \( \text{im} \), zero at the junction between the outer and the inner medulla and \( L_{\text{im}} \) at the papillary tip. The nondimensional coordinate \( x_{\text{im}}/L_{\text{im}} \) thus runs from 0 to 1 between these two limits. The volume fraction of the interstitium in the inner medulla was assumed to vary linearly from 0.1 at \( x_{\text{im}}/L_{\text{im}} = 0.2 \) to 0.3 at \( x_{\text{im}}/L_{\text{im}} = 1 \) (9), so that

\[
A_{\text{im}}(x_{\text{im}}) = A_{\text{im}}(0.25x_{\text{im}}/L_{\text{im}} + 0.05)
\]

Combining the mass balance Eqs. 1–3 with Eqs. 10a–10c, the total amount of water or solute recovered by vasa recta (VRR) is given by (see APPENDIX)

\[
\text{VRR}_{\text{i}} = A_{\text{im}}(0) \int_{0}^{L_{\text{im}}} (0.25x_{\text{im}}/L_{\text{im}} + 0.05)\psi_{\text{i}}(x_{\text{im}}) \, dx_{\text{im}}
\]

where \( i = \text{volume, sodium, urea} \).

Water and solute generation rates. Parameter values for input rates were determined by considering the fractions of filtered volume and solute that are reabsorbed into the inner medullary interstitium. If \( C_{s}^{f} \) is the systemic concentration of solute \( i \) and GFR is the glomerular filtration rate, then the filtered load of solute \( i \) is given by the product \( C_{s}^{f} \cdot \text{GFR} \). Estimates of the fractions of filtered volume, sodium, and urea (\( f_{\text{vo}}, f_{\text{Na}}, \text{and} f_{\text{Na}} \), respectively) that are recovered by vasa recta from the inner medullary interstitium were obtained as follows.

Water and sodium, reabsorbed from the loop of Henle and collecting duct, must be removed from the medullary interstitium by vasa recta. Urea is reabsorbed from the collecting duct and secreted into the loop of Henle; vasa recta must therefore remove only the net difference. Literature estimates of the fraction of volume (\( f_{\text{vo}} \)) and sodium (\( f_{\text{Na}} \)) removed from the collecting duct are given in Table 1. The data for the loop of Henle are both sparse and difficult to interpret. One difficulty is that fractional deliveries of filtered loads repre-
Table 2. Baseline parameter values

<table>
<thead>
<tr>
<th>Parameter data</th>
<th>DVR</th>
<th>AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracellular hydraulic conductivity, $L^p_i$ (cm·s$^{-1}$·mmHg$^{-1}$)</td>
<td>$1.4 \times 10^{-6}$</td>
<td>$12.5 \times 10^{-6}$</td>
</tr>
<tr>
<td>Transcellular osmotic hydraulic conductivity, $L^c_i$ (cm·s$^{-1}$·mmHg$^{-1}$)</td>
<td>$1.0 \times 10^{-7}$</td>
<td></td>
</tr>
<tr>
<td>Paracellular permeability to sodium, $P_{Na}$ (cm/s)</td>
<td>$75 \times 10^{-5}$</td>
<td>$113 \times 10^{-5}$</td>
</tr>
<tr>
<td>Paracellular permeability to urea, $P_{uc}$ (cm/s)</td>
<td>$75 \times 10^{-5}$</td>
<td>$113 \times 10^{-5}$</td>
</tr>
<tr>
<td>Transcellular (carrier-mediated) permeability to urea, $P_{uc}$ (cm/s)</td>
<td>$285 \times 10^{-5}$</td>
<td></td>
</tr>
</tbody>
</table>

Morphological data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descending vasa recta (DVR) diameter, D (µm)</td>
<td>15.6</td>
</tr>
<tr>
<td>Ascending vasa recta (AVR) diameter, D (µm)</td>
<td>20.0</td>
</tr>
<tr>
<td>Total length of medulla, L (mm)</td>
<td>7.8</td>
</tr>
<tr>
<td>Length of inner medulla, L$_{im}$ (mm)</td>
<td>5.9</td>
</tr>
</tbody>
</table>

References for these parameter values are given in Edwards and Pallone (6, 7).

were made dependent upon position along the corticomedullary axis. The following four cases were examined

\[
\Psi_i(x_{im}) = \Psi_{ic} \quad (14a)
\]
\[
\Psi_i(x_{im}) = \Psi_i(x_{im}, L_{im}) \quad (14b)
\]
\[
\Psi_i(x_{im}) = \Psi_i \exp[a(x_{im}/L_{im} - 1)] \quad (14c)
\]
\[
\Psi_i(x_{im}) = \Psi_i(1 - x_{im}/L_{im}) \quad (14d)
\]

where $\Psi_{ic}$, $\Psi_i$, $\Psi_{im}$, $\Psi_{id}$, and $\alpha$ are given constants. Equations 14a, 14b, 14c, and 14d correspond to a constant, a linear increase, an exponential increase, and a linear decrease along the corticomedullary axis, respectively.

Parameters and computational methods. Parameter values such as morphological data and baseline permeabilities are summarized in Table 2. The GFR was taken as 784 µl/min (35), and we assumed systemic concentrations of sodium and urea of 150 and 5 mmol/l (or µmol/cm$^3$), respectively. Hence, the filtered loads of water, sodium, and urea are $1.3 \times 10^{-2}$ cm$^3$/s, 2.0 µmol/s, and $6.5 \times 10^{-2}$ µmol/s, respectively. At the corticomedullary junction in DVR, the hematocrit was taken to be 0.25 and the single-vessel blood flow rate ($q_0$) values of flow rates and permeabilities were assumed to be 1.0% and 40.0%, respectively (i.e., $2.0 \times 10^{-2}$ µmol/s and $2.6 \times 10^{-2}$ µmol/s). The interstitial area-weighted generation rate of water in the inner medulla was decreased linearly from its maximum value at the junction between the outer and inner medulla to zero at the papillary tip, whereas that of sodium was increased linearly between these two points. The interstitial area-weighted input rate of urea was increased exponentially, to reflect the fact that urea appears to be secreted in the interstitium mostly toward the papillary tip; specifically, we assumed that $\Psi_u$ is proportional to $\exp[6(x_{im}/L_{im} - 1)]$. The corresponding values of $\Psi_w$, $\Psi_{Na}$, and $\Psi_u$ are given in Table 3. Those assumptions are further discussed below.

Based upon these parameters, variations in plasma flow rate and in sodium and urea concentrations along the corticomedullary axis are illustrated in Figs. 1-4. Shown in Figs. 1 and 2 are the overall and single-vessel plasma flow rates, respectively. Starling forces favor volume uptake through the paracellular pathway. However, when small solutes, to which water channels are impermeable, are more concentrated in the interstitium than in DVR, the transcellular volume flux across DVR water channels is directed toward the interstitium, resulting in fluid loss. The model predicts that DVR plasma flow decreases along the corticomedullary axis, both overall and in each vessel, except near the papillary tip. Efflux from DVR stems from the significant sodium and urea interstitium-to-DVR con-

Table 3. Inner medullary interstitial area-weighted generation rates with $f_w = 1\%$, $f_{Na} = 1\%$, and $f_{ur} = 40\%$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Water, $s^{-1}$</th>
<th>Sodium, µmol·cm$^{-3}·s^{-1}$</th>
<th>Urea, µmol·cm$^{-3}·s^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear decrease from $x_{im} = 0$ to $L_{im}$</td>
<td>$\Psi_{id} = 1.90 \times 10^{-2}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>$\Psi_{ic} = 7.24 \times 10^{-3}$</td>
<td>$\Psi_{Na} = 1.09$</td>
<td>$\Psi_{id} = 1.45$</td>
</tr>
<tr>
<td>Linear increase from $x_{im} = 0$ to $L_{im}$</td>
<td>$\Psi_{il} = 1.16 \times 10^{-2}$</td>
<td>$\Psi_{Na} = 1.75$</td>
<td>$\Psi_{id} = 2.33$</td>
</tr>
<tr>
<td>Exponential increase from $x_{im} = 0$ to $L_{im}$ (a = 6)</td>
<td>$\Psi_{ie} = 4.41$</td>
<td>$\Psi_{Na} = 5.88$</td>
<td></td>
</tr>
</tbody>
</table>

See Eqs. 14a–14d for an explanation of symbols.
centration gradients (see below). Conversely, the AVR plasma flow rate increases as blood flows back toward the corticomedullary junction: AVR in the inner medulla must recover both the water generated in the interstitium (i.e., from nephron loops) and that which is driven out from DVR; in the vascular bundles of the outer medulla, only the latter term is present. Near the papillary tip, there is no or very little water generated into the interstitium, and the force balance favors a slight volume efflux from AVR, necessarily accompanied by a parallel influx into DVR. Overall, most of the water recovered by vasa recta is taken up by AVR, and the AVR-to-DVR blood flow rate ratio is 1.14 at the corticomedullary junction. The interstitial hydraulic pressure (P_I) drops from about 1 mmHg at the corticomedullary junction to 211 mmHg at the papillary tip.

Sodium and urea concentrations are plotted as a function of medullary depth in Figs. 3 and 4, respectively. In both cases, the increase in DVR plasma concentrations follows the increase in interstitial concentrations, albeit with some delay, since permeabilities are finite and the countercurrent exchanger is not ideal. As plasma flows back up AVR, the decrease in CNa and Cu is parallel to that in the interstitium but also slower (curves corresponding to interstitial concentrations are not shown for clarity; they would be in between those for DVR and AVR). As described in Edwards and Pallone (6, 7), the concentration rise in outer medullary DVR (OMDVR) is accentuated by the sieving of small solutes by AQP1 water channels. In the inner medulla (IM), starting from the junction between the outer and inner medulla, concentrations increase slowly at first and then more rapidly, parallel with the rise in interstitial area-weighted solute generation rates (as described above, ΨNa and Ψu increase linearly and exponentially, respectively). This effect is enhanced by the fact that the amount of water generated into the IM interstitium is progressively smaller, as Ψw decreases linearly along the corticomedullary axis. Near the papillary tip, concentrations reach a small plateau due to the slight water influx into DVR (see above). The total osmolality at the papillary tip is 1.470 mosmol/kgH2O, 47% of which is due to urea. Because C_u must increase from 5 mmol/l initially in DVR to about 700 mmol/l at the papillary tip (vs. 150 to about 400 for CNa), the AVR-to-DVR concentration ratio at the corticomedullary junction is six times as high for urea as it is for sodium. Indeed, when axial (corticomedullary) gradients are steep, transmural gradients must also increase to give rise to the large solute fluxes that are needed to concentrate and then dilute plasma.

Because of the large permeability of vasa recta to sodium and urea, diffusion is the predominant mechanism by which these small solutes are transported across the vessels. The Peclet number for sodium and urea ranges from 10⁻² to 10⁻¹, and Eq. 6 could be approximated by the classic Kedem-Katchalsky equations. Convection plays a more significant role in the

![Fig. 1. Ratio of total plasma flow rate (Q_P) to initial descending vasa recta (DVR) blood flow rate as a function of position along the corticomedullary axis (x). L represents the total length of the medulla. Junction between outer medulla and inner medulla corresponds to x/L = 0.24. Effects of increasing the initial blood flow rate in a single DVR from 10 to 20 nl/min (B) and hydraulic conductivity of DVR from 1.4 x 10⁻⁶ to 3.4 x 10⁻⁶ cm·s⁻¹·mmHg⁻¹ (C) are shown relative to the baseline case (A). Generation rates for water, sodium, and urea are those of the baseline case.](http://ajprenal.physiology.org/)

![Fig. 2. Ratio of single-vessel plasma flow rate (q_P = Q_P/N) to initial single DVR blood flow rate as a function of position in DVR and AVR. Effects of increasing the initial blood flow rate from 10 to 20 nl/min (B) and hydraulic conductivity of DVR from 1.4 x 10⁻⁶ to 3.4 x 10⁻⁶ cm·s⁻¹·mmHg⁻¹ (C) are shown relative to the baseline case (A). Generation rates for water, sodium, and urea are those of the baseline case. Discontinuity at the papillary tip is due to the fact that each DVR gives rise to 2.25 AVR.](http://ajprenal.physiology.org/)

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**References:**


transport of albumin, for which the Peclet number is between $5 \times 10^{-2}$ and 15.

Water generation rate. To assess the validity of our baseline case assumptions, we first modified the distribution of the area-weighted generation rate of water ($C_{w}$), without changing the overall amount of water recovered by vasa recta (i.e., $f_{w} = 1.0\%$). The input rates for sodium and urea were exactly as in the baseline case (see Table 3 for values). If the area-weighted generation rate of water in the inner medullary interstitium is kept constant with depth, then plasma concentrations increase much less than in the baseline case, as shown in Figs. 3 and 4, even though the total amount of water that has to be recovered by vasa recta remains the same. Since water is generated at a constant rate throughout the IM rather than preferentially toward the tip, smaller interstitium-to-DVR sodium concentration gradients result in less volume efflux from DVR, so that sodium concentrations increase slightly less than in the baseline case (results not shown). With a constant $\Psi_{Na}$, the osmolality at the papillary tip is 1,155 mosmol/kgH$_2$O, with a 51% contribution from urea. Conversely, if the area-weighted generation rate of sodium increases exponentially along the corticomedullary axis like that of urea, then $C_{Na}$ rises very steeply in the inner medulla as illustrated in Fig. 5; there is then more water efflux from DVR, urea concentrations increase slightly more relative to the baseline case, and the tip osmolality is 2,205 mosmol/kgH$_2$O, 35% of which is due to urea. With this assumption, however, $P_{I}$ is found to be lower than $-20$ mmHg at the papillary tip.

Results corresponding to a constant area-weighted generation rate of water are shown in Fig. 6. Even when $\Psi_{Na}$ increases exponentially along the corticomedullary axis, plasma sodium concentrations remain lower than in the baseline case, and the osmolality at the papillary tip is only 915 mosmol/kgH$_2$O, with a 40% contribution from urea.

Urea generation rate. Assuming an exponential increase in the area-weighted generation rate of urea as in the baseline case, we then examined the effect of changes in the rate of increase by varying the multiplying factor $\alpha$ in the expression for $\Psi_{u}$ (Eq. 14c). The rise in plasma sodium concentration is much smaller than in the baseline case (Fig. 5), since sodium is being generated at the same rate throughout the IM rather than preferentially toward the tip. Smaller interstitium-to-DVR sodium concentration gradients result in less volume efflux from DVR, so that urea concentrations increase slightly less than in the baseline case (results not shown).

**Fig. 3.** Ratio of plasma sodium concentration ($C_{Na}$) to its initial concentration in DVR ($C_{Na0}$) as a function of position, assuming that the area-weighted generation rate of water in the inner medullary (IM) interstitium decreases linearly with $x$ (A, baseline case), remains constant (B), or increases linearly (C). Fraction of filtered load recovered by vasa recta is equal to 1% for water, 1% for sodium, and 40% for urea.

**Fig. 4.** Ratio of plasma urea concentration ($C_{u}$) to the initial sodium concentration in DVR ($C_{Na0}$) as a function of position, assuming that the area-weighted generation rate of water in the IM interstitium decreases linearly with $x$ (A, baseline case), remains constant (B), or increases linearly (C). Fraction of filtered load recovered by vasa recta is equal to 1% for water, 1% for sodium, and 40% for urea.
assumptions regarding input rates for water and sodium were those of the baseline case, and the fraction of filtered urea that is recovered by vasa recta ($f_u$) was maintained at 40%. Results for urea are shown in Fig. 7. As expected, the steeper the increase in $C_u$, the greater the rise in inner medullary urea concentration and the higher the tip osmolality. Assuming that $C_u = C_{u0} \exp(\Delta x/L_{IM} - 1)$, the osmolality at the papillary tip is only 1,110 mosmol/kgH$_2$O, 36% of which is due to urea. With $C_u = C_{u0} \exp[\Delta x/L_{IM} - 1]$, the tip osmolality is as high as 2,055 mosmol/kgH$_2$O, with a 55% contribution of urea. In the latter case, however, PI is about 15 mmHg at the papillary tip. As $\omega$ is increased, interstitial-to-DVR urea concentration gradients become larger so that there is more water efflux from DVR; plasma sodium concentrations are thus slightly raised as well (results not shown).

Variations in the functional form of $C_u$ were then examined. The overall amount of urea recovered by vasa recta was kept constant (i.e., $f_u = 40\%$), and the input rates for water and sodium were those of the baseline case. As expected, if $C_u$ increases linearly rather than exponentially in the inner medulla, then the rise in $C_u$ is more moderate, as illustrated in Fig. 8. Because of smaller interstitium-to-DVR urea concentration gradients, water efflux from DVR is reduced and plasma sodium concentrations are also slightly lower than in the baseline case. The osmolality at the papillary tip is then only 1,110 mosmol/kgH$_2$O, with a 35% contribution from urea. These effects are even more pronounced when $\Psi_u$ remains constant (Fig. 8). In this case, the tip osmolality is 955 mosmol/kgH$_2$O, 28% of which is due to urea.

Results corresponding to a constant area-weighted input rate of water are shown in Fig. 9. If the interstitial area-weighted generation rate of urea is also assumed to remain constant along the corticomedullary axis, then urea concentrations actually decrease slightly in the inner medulla. Indeed, since water is generated throughout the inner medullary interstitium and since interstitium-to-DVR urea concentration gradients are lower, the driving force balance favors volume influx into DVR in the IM, diluting both sodium and urea. When $C_u$ is taken to increase linearly along the corticomedullary axis, the concentration of urea overall increases slightly in the inner medulla, as shown in Fig. 9. With a constant $C_u$, the osmolality at the papillary tip is found to be 535 mosmol/kgH$_2$O; with a linear $C_u$, it is 600 mosmol/kgH$_2$O (the contribution of urea is then 24 and 34%, respectively).

Blood flow rate variations. We then examined the sensitivity of our results to perturbations in flow rates and permeabilities. Assumptions regarding input rates were those of the baseline case. Effects of changes in the initial blood flow rate are illustrated in Figs. 1 and 2.

![Fig. 5. Effect of changes in distribution of interstitial sodium on sodium concentration, assuming that the interstitial area-weighted generation rate of water decreases linearly with $x$ in the IM. Ratio of plasma sodium concentration ($C_{Na0}$) to its initial concentration in DVR ($C_{NaDVR}$) is plotted as a function of position. Area-weighted generation rate of sodium in the IM interstitium is assumed to be constant (A), to increase linearly (B, baseline case), or to increase exponentially (C). Fraction of filtered load recovered by vasa recta is equal to 1% for water, 1% for sodium, and 40% for urea.](http://ajprenal.physiology.org/)

![Fig. 6. Effect of changes in distribution of interstitial sodium on sodium concentration, assuming that the interstitial area-weighted generation rate of water remains constant in the IM. Ratio of plasma sodium concentration ($C_{Na0}$) to its initial concentration in DVR ($C_{NaDVR}$) is plotted as a function of position. Area-weighted generation rate of sodium in the IM interstitium is assumed to be constant (A), to increase linearly with $x$ (B), or to increase exponentially (C). Fraction of filtered load recovered by vasa recta is equal to 1% for water, 1% for sodium, and 40% for urea.](http://ajprenal.physiology.org/)
The single DVR blood flow rate at the corticomedullary junction was increased to 20 nl/min, that is, to twice its value in the baseline case (10 nl/min). With a higher initial plasma flow rate, changes in solute concentration are slower, so that CNa and Cu remain lower and transmural volume efflux from DVR is reduced, as shown in Fig. 2. As expected, the total osmolality at the papillary tip varies inversely with the efferent blood flow rate (Table 4).

Permeability variations. DVR (paracellular) hydraulic conductivity was determined by Pallone et al. (24) as $1.4 \times 10^{-2}$ cm$^{-2}$ s$^{-1}$ mmHg$^{-1}$. However, the authors indicated that this value represents a lower bound, because Starling forces may have been overpredicted; an upper limit estimate of $3.4 \times 10^{-3}$ cm$^{-2}$ s$^{-1}$ mmHg$^{-1}$ was suggested. Results corresponding to this upper bound for the paracellular permeability of DVR ($L_p^D$) are shown in Figs. 1 and 2. In the baseline case, as in this case, the DVR paracellular flux is actually positive (i.e., directed toward the interstitium) near the corticomedullary junction, because the transcapillary hydraulic pressure difference is greater than the oncotic pressure gradient (as volume efflux proceeds, proteins will become more concentrated in the lumen, and the balance will be reversed all the way toward the papillary tip). Hence, an increase in $L_p^D$ first results in a greater fluid loss from DVR. Then, as the paracellular flux changes sign, volume influx into DVR is much more significant than in the baseline case. Single-vessel plasma flow rates thus remain consistently higher in the inner medulla, as illustrated in Fig. 2, thereby reducing small solute concentrations and the osmolality at the papillary tip (Table 4). Increasing the paracellular hydraulic conductivity of AVR ($L_p^A$) in a similar way does not produce significant effects, however, as the amount of water taken up by AVR is primarily determined by the interstitial volume generation rate. Rises in $L_p^A$ are essentially translated into reductions in $\Delta P$, i.e., into higher interstitial hydraulic pressures.

We then varied the permeability of vasa recta to sodium or urea, without altering inner medullary input rates. Since the amount of solute recovered by vasa recta remains the same when generation rates are fixed, the smaller concentration difference between AVR and DVR resulting from a higher permeability must be accompanied by an overall increase in concentration or in plasma flow rate. When the permeability of DVR to sodium is doubled, interstitium-to-DVR sodium concentration gradients decrease, thereby reducing volume efflux from DVR through water channels. Plasma flow rates are then higher, thus compensating for the

![Fig. 7. Effects of changes in distribution of interstitial urea on urea concentration, assuming that the interstitial area-weighted generation rate of water decreases linearly with $x$ in the IM. Ratio of plasma urea concentration ($C_{uP}$) to the initial sodium concentration in DVR ($C_{Na0}$) is plotted as a function of position. Area-weighted generation rate of urea in the IM increases exponentially as $\Psi_u = \Psi_{u0} \exp(\alpha (x_{im}/L_{im} - 1)$, and the factor $\alpha$ is varied. Fraction of filtered load recovered by vasa recta is equal to 1% for water, 1% for sodium, and 40% for urea. Results are given for $\alpha = 2, 4, 6, 8, \text{and } 10$. Corresponding values of $\Psi_{u0}$ are 2.73, 4.26, 5.88, 7.53, and 9.20 µmol·cm$^{-2}$·s$^{-1}$, respectively.](http://ajprenal.physiology.org/)

![Fig. 8. Effect of changes in distribution of interstitial urea on urea concentration, assuming that the interstitial area-weighted generation rate of water decreases linearly with $x$ in the IM. Ratio of plasma urea concentration ($C_{uP}$) to the initial sodium concentration in DVR ($C_{Na0}$) is plotted as a function of position. Area-weighted generation rate of urea in the IM interstitium is assumed to be constant (A), to increase linearly with $x$ (B), or to increase exponentially (C, baseline case). Fraction of filtered load recovered by vasa recta is equal to 1% for water, 1% for sodium, and 40% for urea.](http://ajprenal.physiology.org/)
Varying the paracellular permeability of DVR to urea does not affect volume efflux from DVR as much as a similar change in the permeability to sodium does, since a large fraction of urea is transported by carriers in DVR. When the permeability of DVR or AVR to urea is raised, \( C_u \) increases in AVR and DVR to compensate for the smaller transmural gradients. As expected, increases (2-fold) in vasa recta permeability to small solutes yield higher osmolality at the papillary tip (Table 4).

Corticomedullary variations of transport properties. We assumed in this study that permeability values are the same in outer and inner medullary vasa recta (Table 2). Although the average permeability to sodium \( P_{Na} \) of OMDVR and IMDVR is \( 75 \times 10^{-5} \text{ cm/s} \) by in vitro and in vivo microperfusion (24), some DVR have a very low \( P_{Na} \). It is also likely that \( P_{Na} \) measurements in IMDVR were underestimated due to boundary layer effects on isotope efflux (24). To investigate the effect of axial variations in the permeability of DVR to sodium, we increased \( P_{Na} \) from \( 10 \times 10^{-5} \text{ cm/s} \) at the corticomedullary junction to \( 150 \times 10^{-5} \text{ cm/s} \) at the papillary tip along DVR, then compared the results to simulations in which DVR \( P_{Na} \) remains uniform and equal to \( 75 \times 10^{-5} \text{ cm/s} \) throughout the medulla. Increasing the permeability of DVR to sodium along the corticomedullary axis results in more water efflux from OMDVR and less from IMDVR. Indeed, the more permeable the vessels, the smaller the interstitium-to-DVR concentration gradients, the smaller the driving force for volume efflux through AQP1 water channels, and vice versa. At the papillary tip, the plasma flow rate is the same as in the baseline case, but sodium concentrations are higher and the total osmolality is about 1,640 mosmol/kgH\(_2\)O (vs. 1,470 in the baseline case). Hence, a gradual increase in sodium permeability along the corticomedullary axis seems to enhance the osmolar gradient in the inner medulla.

Although there is evidence that the permeability to sodium of OMDVR and IMDVR may be different (24), the data concerning urea are more difficult to interpret. Whereas permeability measurements by Pallone et al. (24) suggested the presence of a facilitated transport pathway for urea in OMDVR only, more recent in situ hybridization experiments have shown that the UT3 urea transporter is expressed in IMDVR as well (33). Boundary layer effects may have limited the in vivo microperfusion experiments of Pallone et al. (24), and it is difficult to speculate on the axial variations of DVR permeability to urea. As for water, the paracellular hydraulic conductivity of DVR appears to be the same in the outer medulla (34) and the inner medulla (23); there is no evidence that AQP1 expression (and hence the transcellular hydraulic conductivity of DVR) varies with axis either. Finally, measurements of the paracellular hydraulic conductivity of AVR have been limited to the inner medulla.

**DISCUSSION**

This model of medullary microvascular exchange incorporates variable water and solute generation rates.
in the medullary interstitium as a means of accounting for deposition of solutes and water by nephrons and the collecting duct. Complete transport equations are employed to simulate the coupling between microvascular transport of solutes and water. The current model follows the lead of Wang and co-workers (36, 37), who developed a model of microvascular exchange in which a countercurrent capillary loop is embedded in a secretory epithelium. They obtained elegant analytic solutions that reproduced the exponential corticomedullary gradient described by Koeppel et al. (11). The desire to obtain a closed solution and thereby avoid numerical integration necessitated several constraints. In contrast, we have accepted the need for extensive numerical computation to enable exploration of the coupling of solvent and solute transport, water channels, facilitated urea transport, RBC and paracellular fluxes, variations in the number of vessels, and complex spatial profiles of solute and water generation rates.

Interstitial generation rates. The principal finding of this study is that the smaller \( f_v \) and the higher \( f_{Na} \), the greater the osmolality predicted at the papillary tip. We have chosen a value of 1\% for \( f_v \), which is also consistent with the theoretical work of Wexler et al. (39) and Stephenson et al. (31). Our choice of \( f_{Na} \) was restricted with the theoretical work of Wexler et al. (39) and Stephenson et al. (31). Our choice of \( f_{Na} \) was restricted to upper limits in the antidiuretic rat kidney. For instance, if \( f_{Na} \) is only 20\%, we conclude that the contribution of urea to papillary tip osmolality is close to 50\% (22). A value of 1\% was found to be the maximum value that satisfied that requirement. The fraction of filtered urea that is recovered by vasa recta, \( f_{ur} \), was chosen as 40\% to achieve a papillary tip osmolality of about 1,500 mosmol/kgH_2O, assuming that the interstitial area-weighted generation rate for water decreases linearly along the corticomedullary axis while those for sodium and urea increase linearly and exponentially, respectively. This value for \( f_{ur} \) is well within the range of numbers used in other modeling studies (see METHODS), but is possibly close to upper limits in the antidiuretic rat kidney. Reducing \( f_{ur} \) in this model to 20\%, as obtained by Thomas (32), would reduce the predicted papillary tip interstitial concentration and osmolality (the latter by about 30\%). If \( f_{ur} \) is only 20\%, we conclude that \( \Psi_v \) needs to fall more sharply or that \( \Psi_i \) has to rise more rapidly along the medullary axis than specified by Eqs. 14c-14d for high interstitial osmolalities to exist at the papillary tip of the antidiuretic kidney.

Table 1 suggests that the fraction of filtered sodium that is recovered between the base and the tip of the papilla (i.e., about a third of the inner medulla) by vasa recta from the collecting duct alone is about 0.5\%. Besides, Henle’s limbs contribute an additional, unknown amount. Hence our baseline estimate of 1\% for the overall amount of sodium recovered by vasa recta may be too low. The effects of increasing \( f_{Na} \) up to 2\% are summarized in Table 5. Multiplying the fractional recovery of filtered sodium by a given factor increases the papillary tip concentration of sodium by roughly the same factor. Since the amount of urea recovered by the microcirculation is kept constant, the fraction of the papillary tip osmolality that is due to urea falls sharply, from 47\% (\( f_{Na} = 1\% \)) to 36\% (\( f_{Na} = 1.5\% \)) to 30\% (\( f_{Na} = 2\% \)). It is therefore difficult to reconcile the experimental data in Table 1, which suggest a higher recovery of sodium by vasa recta, with measurements of the relative contribution of urea to the osmolar gradient, about 50\% at the papillary tip (22). Using our baseline case assumptions, the osmolality at the papillary tip is predicted to be 1,470 mosmol/kgH_2O. With \( f_{Na} = 2\% \), it increases to about 2,300 mosmol/kgH_2O. If the fraction of filtered water recovered by vasa recta is simultaneously increased to 2\%, then the papillary tip osmolality drops significantly, to 1,040 mosmol/kgH_2O; with \( f_{Na} = 2\% \) and \( f_{Na} = 1\% \), it is found to be 700 mosmol/kgH_2O.

Our baseline case predicts that the fraction of filtered water recovered by the microcirculation between the papillary base and tip ranges from 0.02\% when \( \Psi_v \) decreases linearly to 0.05\% when \( \Psi_v \) is constant (per unit cross-sectional area of the interstitium). Higher values of \( f_v \) are more consistent with experimental data obtained from micropuncture and microcatheterizations of the collecting duct (Table 1). It should be noted, however, that the majority of those studies were performed after ureteral excision. Excision of the ureter in the rats lowers urinary concentrating ability from a maximum of \(-3,000\) to less than \(900\) mosmol/kgH_2O (4, 22, 26, 40), well below the predictions of our baseline case simulations. Assuming that the fraction of filtered water recovered by vasa recta (\( f_{ur} \)) is 1\%, the AVR-to-DVR blood flow rate ratio is found to be 1.1 at the corticomedullary junction and also 1.1 at the base of the papilla, i.e., about 2 mm from the papillary tip. Zimmerhackl et al. (41) found a somewhat higher blood flow rate ratio of 1.2 at the base of the papilla, implying greater volume uptake by the microcirculation within the papilla. Those studies employed videomicroscopic observation and micropuncture of the vessels on the surface of the papilla, necessitating excision of the ureter, and likely yielded papillary tip osmolalities lower than predicted by this model.

Interestingly, a low value for \( f_v \) (i.e., 1\%) leads to high papillary tip osmolality but yields computations of negative papillary interstitial pressure. Negative interstitial pressures are obtained because transport rates of water across the highly conductive AVR wall are low when \( f_v \) is 1\%, so that negative pressures are required to limit transmural water influx to that which preserves local mass balance. Higher values for \( f_v \) yield

### Table 5. Effect of variations in vasa recta recovery of sodium on small solute axial concentration gradients

<table>
<thead>
<tr>
<th>( f_{Na} )</th>
<th>Plasma sodium concentration at papillary tip, C_Na ( (x = 1) )</th>
<th>Total osmolality at papillary tip, mosmol/kgH_2O</th>
<th>Fraction of osmolality at papillary tip due to urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0%</td>
<td>390</td>
<td>1,470</td>
<td>0.47</td>
</tr>
<tr>
<td>1.5%</td>
<td>595</td>
<td>1,865</td>
<td>0.36</td>
</tr>
<tr>
<td>2.0%</td>
<td>805</td>
<td>2,305</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Filtered fractions of water and urea that are recovered by vasa recta are 1\% and 40\%, respectively. Area-weighted generation rates are spatially distributed as in the baseline case.
predictions of positive interstitial pressures. Attempts to experimentally measure pressure in the interstitium of the exposed papilla after ureteral excision yielded positive values, close to the hydraulic pressure in the AVR lumen (21). MacPhee and Michel (16) have suggested that interstitial hydraulic pressure in excess of that in AVR might be required to drive renal medullary AVR volume uptake.

The negative values predicted by our model may be to some extent the result of our simplified hypothesis regarding concentration polarization. If we were to assume that the accumulation of protein during fluid uptake completely eliminates all oncotic pressure differences across AVR walls (i.e., use Eq. 8 rather than Eq. 9), then hydraulic interstitial pressures would be positive, close to the hydraulic pressure in AVR which is fixed at 7.8 mmHg. This assumption, however, leads to occasional inconsistencies as discussed above, as when AVR fluxes are too small to render polarization significant. A more rigorous treatment of concentration polarization, which would include taking into consideration changes in the AVR reflection coefficient to albumin along the corticomedullary axis, would be needed to clarify this issue. Another possible explanation involves the fact that the ureter undergoes rhythmic contractions that intermittently squeeze the papilla. Based on the predictions of this model, we are led to speculate that ureteral contractions may serve to drive water flux into the AVR lumen by raising interstitial pressure, followed by a period of negative interstitial pressure that arises during the relaxation phase. Such periodic reabsorption would allow time for interstitial-to-AVR gradients of albumin, which accumulates on the interstitial side of the barrier results in canceling the interstitial-to-DVR sodium concentration difference across AVR walls (17), and further mathematical simulations are needed to address this issue.

Concentration profiles. Our results indicate that sodium and urea concentrations increase exponentially in the inner medulla, as observed by Koepsell et al. (11), whenever the ratio of the interstitial area-weighted generation rate of small solutes to that of water increases steadily along the corticomedullary axis. This requirement is satisfied when $\psi_0$ is constant while $\psi_w$ and $\psi_u$ increase from the junction between the outer and inner medulla toward the papillary tip, or when the area-weighted generation rate of water is the only one that decreases in the inner medulla. In addition, for a given amount of filtered water and solutes that is recovered by vasa recta overall, the more evenly the solutes are distributed in the interstitium, the smaller the rise in capillary concentrations along the corticomedullary axis, and the lower the osmolality at the papillary tip. Sands and Knepper (27) have reported that the inner medullary collecting duct is more permeable to urea in its distal two-thirds, thus supporting the hypothesis that urea is preferentially reabsorbed toward the papillary tip.

Water and solute transport coupling. The existence of water channels that are totally impermeable to solutes results in significant coupling between the transport of water, sodium, and urea. Although the reflection coefficient of the paracellular pathway to sodium and urea is zero, that of the transcellular pathway is unity, so that concentration gradients across DVR walls will induce water fluxes. Hence, an increase in the permeability of AVR to sodium will also affect urea, because the larger interstitium-to-DVR sodium concentration difference in the outer medulla leads to more volume efflux from DVR through water channels and thus to a more rapid increase in urea concentrations. Conversely, if both water and urea are recovered into AVR at a constant rate throughout the inner medulla, then transcapillary oncotic pressure differences become the dominant driving force for water transport across DVR, and volume influx into DVR occurs throughout the inner medulla, thereby reducing plasma sodium concentrations significantly as well. The presence of a transcellular pathway for water thus makes the concentration profiles of sodium and urea highly interdependent.

Limitations. The model described above takes into account volume and small solute generation rates in the inner medullary interstitium. Its main limitation concerns the transport of albumin and concentration polarization. To rigorously account for the latter, radial variations in fluid velocity and concentrations would need to be considered, which would greatly increase the complexity of the model. Instead, we assumed in this study that polarization is only significant at the AVR wall, where fluid uptake from the interstitium can be very large, and that the accumulation of albumin on the interstitial side of the barrier results in canceling albumin oncotic pressure differences across AVR (Eq. 9). We did not attempt either to elucidate the source of albumin in the medullary interstitium and instead fixed the interstitial concentration of albumin. Several studies have shown that albumin is present in the interstitium in significant concentrations (15, 20), but the mechanisms by which this extravascular pool of albumin is generated and maintained remain to be understood. Pallone (20) suggested that DVR are the source of interstitial proteins and that convective rather than diffusive processes govern the accumulation of albumin in the interstitium. It is possible in principle to maintain steady fluxes of albumin from DVR through the interstitium to AVR (17), and further mathematical simulations are needed to address this issue.

In summary, our results suggest that the ratio between the interstitial area-weighted generation rate of small solutes to that of water must increase along the corticomedullary axis to build an exponential osmolar gradient in the inner medulla. Predicted concentration gradients are especially steep if the input rate of water per unit interstitial area is the only one that decreases along the corticomedullary axis. The inner medullary osmolar gradient can also be improved by reducing medullary blood flow, decreasing the hydraulic conductivity of DVR, and increasing the permeability of vasa recta to sodium and urea.
APPENDIX

Derivation of the total amount of water or solute recovered by vasa recta. Conservation equations for the total blood flow rate, \(Q^B = Q^P + Q^R\), can be written as

\[
\frac{dQ_{avr}}{dx} = - \left( \int_{avr} \frac{\phi_{avr} N_{avr} \pi D_{avr}}{N_{avr}} + \phi_{avr} N_{avr} \pi D_{avr} + A_{int} \psi_v \right) \frac{dN_{avr}}{dx} \tag{A1}
\]

\[
\frac{dQ_{dvr}}{dx} = \left( \int_{dvr} \frac{\phi_{dvr} N_{dvr} \pi D_{dvr}}{N_{dvr}} + \phi_{dvr} N_{dvr} \pi D_{dvr} + A_{int} \psi_v \right) \frac{dN_{dvr}}{dx} \tag{A2}
\]

As described above, the sum of the transmural volume fluxes from DVR and AVR, weighted according to their respective surface area, must be equal and opposite to the rate of water generation in the interstitium

\[
\left( \int_{avr} \phi_{avr} N_{avr} \pi D_{avr} + \int_{dvr} \phi_{dvr} N_{dvr} \pi D_{dvr} + A_{int} \psi_v \right) = 0 \tag{A3}
\]

Subtracting Eq. A1 from Eq. A2 and replacing the terms involving fluxes using Eq. A3 yields

\[
\frac{d(Q_{avr} - Q_{dvr})}{dx} = \left( \frac{Q_{avr}^{B}}{N_{avr}} - \frac{Q_{dvr}^{B}}{N_{dvr}} \right) \frac{dN_{avr}}{dx} - A_{int} \psi_v \tag{A4}
\]

Let \(N = N_{avr}\), and \(dQ = (Q_{avr}^{B} - Q_{dvr}^{B})/N\), then

\[
\frac{dN}{dx} \left( \frac{dN_{avr}}{dx} \right) = \frac{1}{N_{avr}} \frac{dN_{avr}}{dx} \tag{A5}
\]

Equation A4 can be rewritten as

\[
\frac{d(N dQ)}{dx} = dQ - A_{int} \psi_v \tag{A6}
\]

from which it follows that

\[
\frac{dN}{dx} = - A_{int} \psi_v \tag{A7}
\]

We may conclude that

\[
\Delta q(x) = \Delta q(L) - \int_{x}^{L} A_{int}(x) \psi_v(x) \frac{dx}{N'(x)} \tag{A8}
\]

\[
= \int_{x}^{L} A_{int}(x) \psi_v(x) \frac{dx}{N'(x)} \tag{A8}
\]

\[
Q_{avr}^{B}(x) - Q_{dvr}^{B}(x) = N(x) \int_{x}^{L} A_{int}(x) \psi_v(x) \frac{dx}{N'(x)} \tag{A9}
\]

In the outer medulla, \(\psi_v\) is zero. In the inner medulla, the number of DVR is given by (7)

\[
N(x_{im}) = \frac{F_{avr} A_{int}(x_{im})}{[(D_{avr})^2 + 2.25(D_{avr})^2] \pi / 4} \tag{A10}
\]

where \(F_{avr} = 0.3\) is the fraction of the inner medullary interstitium occupied by vasa recta (7). Hence, Eq. A9 can be rewritten as

\[
Q_{avr}^{B}(x_{im}) - Q_{dvr}^{B}(x_{im}) = A_{int}(x_{im}) \int_{x_{im}}^{L} A_{int}(x) \psi_v(x) \frac{dx}{N'(x)} \tag{A11}
\]

The total volume recovered by vasa recta, \(VRR_v\), is then given by

\[
VRR_v = Q_{avr}^{B}(0) - Q_{dvr}^{B}(0) = A_{int}(x_{im} = 0) \int_{0}^{L} (0.25 x'/L_{im} + 0.05) \psi_v(x') \frac{dx'}{N'(x')} \tag{A12}
\]

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Address for reprint requests and other correspondence: A. Edwards, Dept. of Chemical Engineering, Tufts Univ., 4 Colby St., Medford, MA 02155 (E-mail: aedwar01@tufts.edu).

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