The Bohr Effect Is Not a Likely Promoter of Renal Preglomerular Oxygen Shunting

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The aim of this study was to evaluate whether possible preglomerular arterial-to-venous oxygen shunting is affected by the interaction between renal preglomerular carbon dioxide and oxygen transport. We hypothesized that a reverse (venous-to-arterial) shunting of carbon dioxide will increase partial pressure of carbon dioxide and decrease pH in the arteries and thereby lead to increased oxygen offloading and consequent oxygen shunting. To test this hypothesis, we employed a segment-wise three-dimensional computational model of coupled renal oxygen and carbon dioxide transport, wherein coupling is achieved by shifting the oxygen-hemoglobin dissociation curve in dependence of local changes in partial pressure of carbon dioxide and pH. The model suggests that primarily due to the high buffering capacity of blood, there is only marginally increased acidity in the preglomerular vasculature compared to systemic arterial blood caused by carbon dioxide shunting. Furthermore, effects of carbon dioxide transport do not promote but rather impair preglomerular oxygen shunting, as the increase in acidity is higher in the veins compared to that in the arteries. We conclude that while substantial arterial-to-venous oxygen shunting might take place in the postglomerular vasculature, the net amount of oxygen shunted at the preglomerular vasculature appears to be marginal.

Keywords: renal oxygenation, oxygen shunting, carbon dioxide shunting, pH, Bohr effect

INTRODUCTION

Hypoxic conditions in the renal cortex or in the medulla may induce tissue damage and contribute to the pathogenesis of acute and chronic kidney diseases (Evans et al., 2008). It is therefore essential to understand the mechanisms that are involved in the regulation of renal oxygenation. We have shown previously that preglomerular arterial-to-venous (AV) oxygen shunting—a mechanism hypothesized to contribute to the regulation of renal oxygenation (Leong et al., 2007; Evans et al., 2008)—is unlikely to be significant (Olgac and Kurtcuoglu, 2015a,b). Since then the question has arisen whether substantial shunting may nevertheless exist, enabled by the influence of preglomerular carbon dioxide dynamics on oxygen transport. Here we hypothesize that reverse, venous-to-arterial (VA) shunting of carbon dioxide will increase arterial partial pressure of carbon dioxide, decrease pH, and thereby lead to augmented oxygen offloading through the Bohr effect (Kilmartin and Rossi-Bernardi, 1973; Dash et al., 2016) and consequent AV oxygen shunting.
Measurements of renal carbon dioxide partial pressure ($P_{CO_2}$) and pH indicate a wide range of values in various structures of the kidney: In the proximal tubule, $P_{CO_2}$ was measured by Sohtell (1979) to be 60.6 mmHg, by DuBose et al. (1979) 65 mmHg, by Maddox et al. (1984) 57.1–62.1 mmHg, and by De Mello Aires et al. (1990) 35.5 mmHg. In stellate vessels, reported values are 33.7 mmHg (Sohtell, 1979), 65 mmHg (DuBose et al., 1979), 57.1 mmHg (Maddox et al., 1984), and 38.9 mmHg (De Mello Aires et al., 1990). pH of 6.7–7.06 was measured by DuBose et al., 1979. It consists of 7.27 in the proximal tubule and of 65 mmHg (Maddox et al., 1984) where the plasma and RBC velocity profiles and the oxygen concentration in the proximal tubule and of 7.27 in the stellate vessels. De Mello Sohtell, 1979. Schurek et al. (1990) hypothesized that such a mechanism enhances AV oxygen shunting through the Bohr effect. Here we tested this hypothesis incorporating the latest structural data by Ngo et al. (2014) that account for the wrapping of veins around arteries in the preglomerular vasculature. To this end, we extended our previous computational model on renal oxygen transport (Olgac and Kurtcuoglu, 2015a,b) to include carbon dioxide transport. We then coupled oxygen transport to carbon dioxide transport through a function describing the shift of the oxygen-hemoglobin dissociation curve with respect to the local $P_{CO_2}$ and pH as recently described by Dash et al. (2016). The resulting computational model is capable of quantifying $P_{O_2}$, $P_{CO_2}$ and pH as well as fluxes of $O_2$ and $CO_2$ through the vessel walls of wrapped and not-wrapped artery-vein pairs in the preglomerular vasculature. Computations of oxygen transport were performed with a Hill equation with constant $P_{50}$ as well as a variable $P_{50}$ in dependence of the local $P_{CO_2}$ and pH.

**METHODS**

**Model Domain**

The three-dimensional (3D) model domain was previously described in Olgac and Kurtcuoglu (2015a,b). It consists of representative levels corresponding to 11 Strahler orders of the preglomerular vasculature. Each level contains wrapped and not-wrapped artery-vein pairs. The structural information for each level (artery radius, $R_a$, vein radius, $R_v$, number of wrapped and not-wrapped vessels, $k_w$ and $k_nw$, respectively, lumen separation for wrapped and not-wrapped vessels, $L_{sw}$ and $L_{snw}$, respectively, and length of vessels, $l$) is given in Table 1.

**Mathematical Formulation**

Two different sets of equations governing oxygen and carbon dioxide transport dynamics in the renal cortex are solved in the vessels and the tissue. The vessels are composed of a RBC-rich region in the core and a RBC-free region close to the walls. The thickness of the RBC-free region in vessels of each Strahler order is given by $\delta = R + t_{RBC} - \sqrt{R^2 - R_{RBC}^2}$, where $R$ is the vessel radius in that order, and $R_{RBC}$ and $t_{RBC}$ are the radius (4 $\mu$m) and maximum half thickness (1.3 $\mu$m) of a RBC, respectively (Nair et al., 1989). The plasma and RBC velocity profiles and the hematocrit profile in the RBC-rich region, $u_p(r)$, $u_{RBC}(r)$ and $h(r)$, respectively, as well as the plasma velocity profile in the RBC-free region, $u_p(r)$, are calculated as explained in Olgac and Kurtcuoglu (2015a) and set on the computational domain prior to solving the governing equations for oxygen and carbon dioxide transport.

**Oxygen Transport**

For the oxygen transport, we base our calculations on a derivative of our model presented in Olgac and Kurtcuoglu (2015a) where now the variability of $P_{50}$, i.e., the half saturation oxygen partial pressure, is taken into account. Briefly, in the vessels, blood plasma, and RBCs are axially convected. The plasma carries dissolved oxygen and the RBCs carry dissolved and hemoglobin-bound oxygen. Radial diffusion of dissolved oxygen in the plasma is also accounted for. For a variable $P_{50}$ in the RBC-rich region, $P_{O_2}$ is governed by

\[
\frac{\partial P_{O_2}}{\partial z} - h(r)\frac{\partial u_{RBC}(r)}{\partial r}C_{HbT}P_{O_2}P_{O_2} = \partial_P^{O_2}\frac{\partial P_{O_2}}{\partial r} + \partial_{P_{O_2}}^{O_2}\frac{\partial P_{O_2}}{\partial z}, \tag{1}
\]

where $C_{HbT}$, $\alpha_P^{O_2}$ and $\alpha_{RBC}^{O_2}$ are the total heme group concentration in RBCs and the solubility of oxygen in plasma and inside the RBC, respectively (see Data Sheet 1 in Supplementary Material for derivation). The permeability of oxygen in plasma is defined as $K_{O_2} = \alpha_P^{O_2}D_{O_2}^{P}$, where $P_{O_2}$ is the diffusion coefficient of oxygen in plasma. Note that the second term on the left hand side of Equation 1 vanishes for constant $P_{50}$, recovering the original equation developed in Olgac and Kurtcuoglu (2015a). In the RBC-free region, plasma free oxygen concentration follows:

\[
\frac{\partial P_{O_2}}{\partial z} = \frac{\partial_P^{O_2}\frac{\partial P_{O_2}}{\partial r} + \partial_{P_{O_2}}^{O_2}\frac{\partial P_{O_2}}{\partial z}}{\partial_P^{O_2}} \tag{2}
\]

The tissue, together with its capillary vessels, is considered a homogeneous structure in which perfusion and consumption are uniform and dependant on the fractional capillary volume, $\psi$. Both diffusion of free oxygen and advection of free and hemoglobin-bound oxygen along the capillaries are taken into account. The homogeneous tissue oxygen partial pressure, $P_{O_2}$, is governed by Salathe (1982) and Olgac and Kurtcuoglu (2015a):

\[
(1 - \psi)(M_{O_2} + M_{HbO_2}) - \alpha_0^{O_2} P_{O_2}^{T} \nabla \cdot C_{HbT} \frac{\partial P_{O_2}}{\partial z} + \partial_P^{O_2}\frac{\partial P_{O_2}}{\partial r} + \partial_{P_{O_2}}^{O_2}\frac{\partial P_{O_2}}{\partial z} = \alpha_0^{O_2} D_{O_2}^{P} \nabla^2 P_{O_2}. \tag{3}
\]
where $u$, $\alpha_{O_2}^T$, $H_c$, $M_{O_2}$, and $M_{CO_2}$ are the advection velocity of oxygen in capillaries, solubility of oxygen in the tissue, hematocrit in the capillaries, oxygen consumption rate in the tissue and capillary source/sink term, respectively. The permeability of oxygen in tissue is defined such that $K_{O_2}^T = \alpha_{O_2}^T D_{O_2}^T$, where $D_{O_2}^T$ is the diffusion coefficient of oxygen in tissue. Details on how the capillary source/sink term is treated are given in Olgac and Kurtcuoglu (2015a). Advection of oxygen in capillaries is only considered in the tissue between the not-wrapped pairs, since the tissue between the wrapped artery-vein pairs is free of capillaries (Ngo et al., 2014).

In Equations (1–3), $\text{SO}_2$ is the saturation of hemoglobin with oxygen, which is represented by the Hill equation (Clark et al., 1985):

$$\text{SO}_2 = \frac{(P_{O_2}/P_{50})^n}{1+(P_{O_2}/P_{50})^n},$$

where $n$ is an empirical constant. Its derivative with respect to $P_{O_2}$ in Equations (1–3) is given by Olgac and Kurtcuoglu (2015a):

$$\frac{d\text{SO}_2}{dP_{O_2}} = \frac{n(P_{O_2}/P_{50})^n}{P_{O_2}(1+(P_{O_2}/P_{50})^n)^2}.$$  

Equations (1–3) are solved either with a constant $P_{50}$ (as was done in (Olgac and Kurtcuoglu, 2015a)) or with a variable $P_{50}$ that is dependent on local $P_{CO_2}$ and $pH$. $P_{50}$ is varied with respect to local $P_{CO_2}$ and $pH$ according to Dash et al. (2016):

$$P_{50,\Delta pH} = P_{50,S} - 25.535(pH - pH_S) + 10.646(pH - pH_S)^2 - 1.764(pH - pH_S)^3,$$

$$P_{50,\Delta CO_2} = P_{50,S} + 0.1273(P_{CO_2} - P_{CO_2,S}) + 1.083 \cdot 10^{-4}(P_{CO_2} - P_{CO_2,S})^2,$$

$$P_{50} = P_{50,S}\left(\frac{P_{50,\Delta pH}}{P_{50,S}}\right)^{\frac{n\alpha}{n\alpha}},$$

where $P_{50,\Delta pH}$ and $P_{50,\Delta CO_2}$ represent the shifts in $P_{50}$ with respect to pH and $P_{CO_2}$, respectively, and standard physiological values are denoted with "S" for which $P_{50,S} = 26.8 \text{mmHg}$, $pH_S = 7.24$ and $P_{CO_2,S} = 40 \text{mmHg}$ (Dash et al., 2016). Oxygen-hemoglobin dissociation curves under these physiological reference conditions as well as under exemplary acidic and basic conditions are shown in Figure 1.

### Carbon Dioxide Transport

For the carbon dioxide transport, we base our calculations on a modified version of the model presented by Huang and Hellums (1994), accounting, next to oxygen, also for the following seven species: $CO_2$, $H^+_{RBC}$, $HCO_3^{-,RBC}$, $Cl^-_{RBC}$, $H^+_{pl}$, $HCO_3^{-,pl}$ and $Cl^{-,pl}$, namely carbon dioxide as well as hydrogen, bicarbonate and chloride ions in RBC and in plasma, respectively (see Figure 2). In RBCs, we assume chemical equilibrium for the carbon dioxide hydration/dehydration reaction, whereas in plasma we take the reaction term explicitly into account. We present below seven governing equations for these species in the RBC-rich region and refer the reader to the Data Sheet 1 in Supplementary Material for

**TABLE 1 | Structural information at representative levels.**

| Level | $R_v, \mu m$ | $R_a, \mu m$ | $k_{nw}$ | $k_w$ | $L, mm$ | $L_{SW, nw}, \mu m$ | $L_{SW}, \mu m$ | $\varphi$ |
|-------|--------------|--------------|-----------|--------|----------|-----------------|----------------|--------|
| 0     | 0.107        | 0.67         | 0.0536    | 0.1016 | 0.0205   | 0.152           | 0.112          | 0.0518 |
| 1     | 0.147        | 0.102        | 0.0571    | 0.1204 | 0.0416   | 0.112           | 0.112          | 0.0238 |
| 2     | 0.264        | 0.117        | 0.0378    | 0.3870 | 0.0315   | 0.112           | 0.112          | 0.0115 |
| 3     | 0.401        | 0.245        | 0.0170    | 0.1226 | 0.0625   | 0.112           | 0.112          | 0.0115 |
| 4     | 0.583        | 0.297        | 0.0120    | 0.922  | 0.082    | 0.861           | 0.117          | 0.0123 |
| 5     | 0.693        | 0.389        | 0.0105    | 0.91   | 0.861    | 0.861           | 0.117          | 0.0123 |
| 6     | 0.814        | 0.593        | 0.0115    | 0.866  | 0.179    | 0.866           | 0.179          | 0.0099 |
| 7     | 0.774        | 0.85         | 0.173     | 0.179  | 0.0099   | 0.179           | 0.179          | 0.0099 |
| 8     | 0.826        | 0.126        | 0.813     | 0.179  | 0.0099   | 0.179           | 0.179          | 0.0099 |
| 9     | 0.428        | 0.171        | 0.309     | 0.866  | 0.179    | 0.866           | 0.179          | 0.0099 |
| 10    | 0.603        | 0.223        | 0.312     | 0.866  | 0.370    | 0.866           | 0.370          | 0.0099 |

$R_v$, vein radius; $R_a$, artery radius; $k$, no. of vessels; $L$, length of vessels; $LS$, lumen separation; $\varphi$, fractional capillary volume; $nw$, not-wrapped vessels; $w$, wrapped vessels.
their detailed derivation:

\[
\frac{\partial P_{CO_2}}{\partial z} = \alpha_{CO_2}^P \frac{dP_{CO_2}}{dr} \frac{\partial}{\partial r} \left[ \frac{1 - h(r)}{u_P(r)} \right] + \alpha_{RB C}^{P} h(r) u_{RB C}(r) \frac{\partial C_{RB C}}{\partial r} \frac{\partial}{\partial r} \left[ \frac{1 - h(r)}{u_{RB C}(r)} \right]
\]

\[\frac{\partial P_{CO_2}}{\partial z} = \alpha_{CO_2}^P D_{CO_2}^P \frac{\partial}{\partial r} \left[ \frac{1 - h(r)}{u_P(r)} \right] + \alpha_{RB C}^{P} h(r) u_{RB C}(r) \frac{\partial C_{RB C}}{\partial r} \frac{\partial}{\partial r} \left[ \frac{1 - h(r)}{u_{RB C}(r)} \right]
\]

\[\beta_{RB C} \rho_{RB C} \log C_{RB C} + b \rho_{RB C} \log C_{RB C} = \beta_{RB C} \rho_{RB C} \log C_{RB C} + \beta_{RB C} \rho_{RB C} \log C_{RB C} \frac{\partial C_{RB C}}{\partial r} \frac{\partial}{\partial r} \left[ \frac{1 - h(r)}{u_{RB C}(r)} \right]
\]

\[h(r) u_{RB C}(r) \frac{\partial C_{RB C}}{\partial z} = - h(r) J_{HCO_3} \left[ \frac{s}{V} \right]_{RB C}
\]

\[
(1 - h(r)) u_P(r) \frac{\partial C_{H^+}}{\partial r} = \frac{D_{H^+}}{r} \frac{\partial}{\partial r} \left[ \frac{\partial C_{H^+}}{\partial r} \right]
\]

\[+ h(r) J_{HCO_3} \left[ \frac{s}{V} \right]_{RB C}, \quad (11)
\]

\[
(1 - h(r)) u_P(r) \frac{\partial C_{H^+}}{\partial r} = \frac{D_{H^+}}{r} \frac{\partial}{\partial r} \left[ \frac{\partial C_{H^+}}{\partial r} \right]
\]

\[+ 2.303C_{H^+} \frac{\beta_{RB C} \rho_{RB C} \log C_{RB C} + b \rho_{RB C} \log C_{RB C}}{\beta_{RB C} \rho_{RB C} \log C_{RB C} + \beta_{RB C} \rho_{RB C} \log C_{RB C}} \frac{\partial C_{RB C}}{\partial r} \frac{\partial}{\partial r} \left[ \frac{1 - h(r)}{u_{RB C}(r)} \right], \quad (12)
\]

\[
(1 - h(r)) u_P(r) \frac{\partial C_{HCO_3}}{\partial r} = \frac{D_{HCO_3}}{r} \frac{\partial}{\partial r} \left[ \frac{\partial C_{HCO_3}}{\partial r} \right]
\]

\[+ (1 - h(r)) \frac{\partial C_{HCO_3}}{\partial r} - h(r) J_{HCO_3} \left[ \frac{s}{V} \right]_{RB C}, \quad (13)
\]
where \( \alpha^p_{\text{CO}_2} \) and \( \alpha^\text{RBC}_{\text{CO}_2} \) are the solubility of carbon dioxide in plasma and inside the RBC, respectively. \( K^\text{RBC} \) and \( f_{\text{water}} \) are the apparent dissociation constant for \( \text{H}_2\text{CO}_3 \) inside RBC and water fraction of RBC volume, respectively. \( \beta^p \) and \( \beta^\text{RBC} \) are the buffering capacity in plasma and in RBC, respectively. Finally, \( \frac{\alpha^p}{\beta^p} \) is the surface to volume ratio of an RBC. Equation (8) represents the normal non-\( \text{HCO}_3^- \) titration line in the Davenport diagram with buffering capacity \( \beta^\text{RBC} \) as slope and \( b \) as a constant, which is calculated based on systemic arterial blood values of \( \text{C}^\text{RBC}_{\text{HCO}_3^-} = 6.52 \text{mM} \) and \( \text{pH}_{\text{RBC}} = 7.24 \) (Davenport, 1958; Boron and Boulpaep, 2012). The permeability of carbon dioxide in plasma is defined as \( \text{K}^P_{\text{CO}_2} = \alpha^p_{\text{CO}_2} D^p_{\text{CO}_2} \), where \( D^p_{\text{CO}_2} \) is the diffusion coefficient of carbon dioxide in plasma, where \( \text{D}^\alpha_{\text{Cl}^-} \), \( \text{D}^\beta_{\text{H}^+} \), and \( \text{D}^\beta_{\text{HCO}_3^-} \) are the diffusion coefficients of chloride, hydrogen and bicarbonate ions, respectively. \( \text{R}^p_{\text{HCO}_3^-} \) and \( \text{I}^p_{\text{HCO}_3^-} \) are the bicarbonate formation rate in plasma and the anion transporter flux through the RBC membrane (see Data Sheet 1 in Supplementary Material for their calculation). In the RBC-free region, plasma carbon dioxide, hydrogen ion, bicarbonate ion and chloride ion concentration follow, respectively:

\[
\left[ \frac{\alpha^p_{\text{CO}_2}}{u^p_{\text{H}_2\text{O}}(r)} \right] \frac{\partial \text{PCO}_2}{\partial z} = \frac{\alpha^p_{\text{CO}_2}}{r} \frac{\partial}{\partial r} \left( r \frac{\partial \text{PCO}_2}{\partial r} \right) - \text{R}^p_{\text{HCO}_3^-},
\]

\[
u^p(r) \left[ \frac{\partial \text{PCO}_2}{\partial z} \right] = \frac{\partial \text{PCO}_2}{\partial r} \frac{\partial}{\partial r} \left( r \frac{\partial \text{PCO}_2}{\partial r} \right) - \text{R}^p_{\text{HCO}_3^-}.
\]

The vessel walls are assumed impermeable to hydrogen, bicarbonate and chloride ions, since these require active transport, which is not considered significant in the preglomerular vasculature. Consequently, in the tissue, only carbon dioxide diffusion is considered. The tissue carbon dioxide partial pressure, \( \text{P}_{\text{CO}_2} \), is governed by:

\[
\alpha^T_{\text{CO}_2} D^T_{\text{CO}_2} \nabla^2 \text{PCO}_2 = -(1 - \varphi) (\text{M}_{\text{CO}_2} + \text{M}_{\text{C}, \text{CO}_2}),
\]

where \( \alpha^T_{\text{CO}_2} \) is the solubility of carbon dioxide in tissue. The permeability of carbon dioxide in tissue is defined as \( K^T_{\text{CO}_2} = \alpha^T_{\text{CO}_2} D^T_{\text{CO}_2} \), where \( D^T_{\text{CO}_2} \) is the diffusion coefficient of carbon dioxide in tissue. \( \text{M}_{\text{CO}_2} \) and \( \text{M}_{\text{C}, \text{CO}_2} \) are the metabolic carbon dioxide production rate in the tissue and capillary carbon dioxide source/sink term, respectively. Here we assume that all \( \text{CO}_2 \) produced in the tissue is taken up by the capillaries, i.e., \( \text{M}_{\text{C}, \text{CO}_2} = - \text{M}_{\text{CO}_2} \), as explained in the next section. All parameters related to oxygen and carbon dioxide transport dynamics are given in Table 2.

### Table 2 | Parameters used in the study.

| Parameter | Value | References |
|-----------|-------|------------|
| \( C^\text{HbT} \) | 19.01 mol/m³ | Present study |
| \( D^\alpha_{\text{Cl}^-} \) | 1.29 \times 10^{-9} m²/s | Huang and Hellums, 1994 |
| \( D^\beta_{\text{H}^+} \) | 1.76 \times 10^{-9} m²/s | Huang and Hellums, 1994 |
| \( D^\alpha_{\text{HCO}_3^-} \) | 1.76 \times 10^{-9} m²/s | Huang and Hellums, 1994 |
| \( D^\beta_{\text{CO}_2} \) | 9.52 \times 10^{-9} m²/s | Huang and Hellums, 1994 |
| \( D^\beta_{\text{CO}_2} \) | 1.25 \times 10^{-9} m²/s | Huang and Hellums, 1994 |
| \( f_{\text{water}} \) | 0.72 | Huang and Hellums, 1994 |
| \( K^\text{DPG} \) | 1.0 mM⁻¹ | Huang and Hellums, 1994 |
| \( k_{\text{V}} \) | 57.5 s | Huang, 1991 |
| \( k_{\text{T}} \) | 3.5 \times 10⁻⁴ M | Huang, 1991 |
| \( f_{\text{trans}} \) | 5.0 \times 10⁻⁴ s | Huang and Hellums, 1994 |
| \( f_{\text{A}} \) | 0.2 mM⁻¹ | Huang and Hellums, 1994 |
| \( \mu_{\text{RBC}} \) | 4 μm | Nair et al., 1989 |
| \( \nu_{\text{RBC}} \) | 1.3 μm | Nair et al., 1989 |
| \( T_{\text{tot}} \) | 1.0 \times 10⁻⁶ | Huang and Hellums, 1994 |
| \( \text{R}_{\text{RBC}} \) | 163 \times 10⁻¹² m² | Huang and Hellums, 1994 |
| \( \gamma_{\text{H}^+} \) | 1.87 μm⁻¹ | Huang and Hellums, 1994 |
| \( \gamma_{\text{Cl}^-} \) | 1.85 μm/s | Jeong et al., 2006 |
| \( \gamma_{\text{HCO}_3^-} \) | 1.10 μM/mmHg | Christofilorides et al., 1969; Vadapalli et al., 2002 |
| \( \gamma_{\text{CO}_2} \) | 1.33 μM/mmHg | Nair et al., 1990; Vadapalli et al., 2002 |
| \( \gamma_{\text{HCO}_3^-} \) | 1.53 μM/mmHg | Vadapalli et al., 2002; Moschandreou et al., 2011 |
| \( \gamma_{\text{CO}_2} \) | 30.3 μM/mmHg | Huang and Hellums, 1994 |
| \( \gamma_{\text{RBC}} \) | 26 μM/mmHg | Huang and Hellums, 1994 |
| \( \gamma_{\text{HCO}_3^-} \) | 30.3 μM/mmHg | Huang and Hellums, 1994 |
| \( \gamma_{\text{RBC}} \) | 60 mM H⁺/pH | Huang and Hellums, 1994 |
| \( \lambda_{\text{RBC}} \) | 5.77 mM H⁺/pH | Huang and Hellums, 1994 |
| \( \lambda_{\text{H}^+} \) | 0.65 mM⁻¹ | Huang and Hellums, 1994 |
| \( \lambda_{\text{CO}_2} \) | 0.24 mM⁻¹ | Huang and Hellums, 1994 |

**Computational Implementation**

Initially, the advection path of oxygen along capillaries, the hematocrit profile and the plasma and RBC velocity profiles are determined as described in Olgac and Kurtcuoglu (2013a) and set on the 3D computational domain. With all flow fields set, Equations (7)–(17) are solved inside the vessels.
while Equation (18) is solved in the tissue for carbon dioxide transport. The solutions of these two sets of equations are determined concurrently in the 3D computational domain. Once the solutions have been obtained, Equations (1)–(3) are solved in the same 3D domain for oxygen transport either with a constant \( P_{50} \) or with a variable \( P_{50} \) that is dependent on the local \( P_{CO_2} \) and pH. The computations are performed in a time-dependent manner using the Euler method for time discretization. The computations are terminated when steady-state is reached, i.e., when temporal changes in the \( P_{CO_2} \) and pH profiles (for carbon dioxide transport calculations) and in the \( P_{O_2} \) profile (for oxygen transport calculations) at each representative level become negligible. A first order upwind scheme and a second order Gaussian integration scheme with harmonic interpolation for oxygen and carbon dioxide permeability are used for the spatial discretization of divergence and Laplacian terms, respectively. The resulting algebraic system is solved using a pre-conditioned bi-conjugate gradient solver (Ferzinger and Perie, 1998) in Foam-extend-3.1 (Weller et al., 1998; Jasak et al., 2007). The solution is determined on all representative levels simultaneously. Independence of the reported results from the employed spatial discretization was confirmed as detailed in the Data Sheet 1 in Supplementary Material.

**Boundary Conditions**

\( P_{O_2} \) at the inlet of the renal artery is fixed to \( P_{O_2,RA} \). For carbon dioxide transport, at the renal artery inlet, chemical equilibrium of the carbon dioxide hydration/dehydration reaction both in RBC as well as in plasma \((R_{HCO_3^-}^{P},i=a,10 = 0)\) and zero flux of bicarbonate and chloride ions over the RBC membrane \((I_{HCO_3^-}^{P},i,a,10 = 0)\) are assumed, since the renal artery receives fresh systemic blood from the aorta. The inlet boundary condition (BC) values based on systemic arterial blood are listed in Table 3.

For the rest of the inlet BCs, at each representative level throughout the computations, partial pressure of oxygen at the inlet, \( P_{O_2,inlet,i} \) is specified such that the oxygen delivery \( D_{O_2,inlet,i} \) (see Data Sheet 1 in Supplementary Material for calculation) matches the delivery at the outlet of the previous level:

\[
D_{O_2,inlet,i} = D_{O_2,outlet,i+1} \quad \text{for arteries,}
\]

\[
D_{O_2,inlet,i} = D_{O_2,outlet,v,i-1} \quad \text{for veins. (19)}
\]

For carbon dioxide transport, at each representative level throughout the computational domain, partial pressure of carbon dioxide at the inlet, \( P_{CO_2,inlet,i} \), hydrogen ion concentration in RBC at the inlet, \( C_{H^+,inlet,i} \), and bicarbonate ion concentration in RBC at the inlet, \( C_{HCO_3^-}^{RBC,inlet,i} \), are specified such that a new chemical equilibrium is established in RBC at the inlet, with carbon dioxide delivery \( D_{CO_2,inlet,i} \) matching the delivery at the outlet of the previous level:

\[
D_{CO_2,inlet,i} = D_{CO_2,outlet,i+1} \quad \text{for arteries,}
\]

\[
D_{CO_2,inlet,i} = D_{CO_2,outlet,v,i-1} \quad \text{for veins. (20)}
\]

where \( D_{CO_2,inlet,i} \) is the sum of deliveries of \( CO_2 \) in plasma and RBC, hemoglobin-bound \( CO_2 \) and \( HCO_3^- \) in RBC (see Data Sheet 1 in Supplementary Material for calculation).

The remaining boundary conditions, i.e., concentration of chloride ion in RBC at the inlet, \( C_{Cl^-}^{RBC,inlet,i} \), concentration of carbon dioxide in plasma at the inlet, \( C_{CO_2}^{P,inlet,i} \), and concentration of bicarbonate ion in plasma at the inlet, \( C_{HCO_3^-}^{P,inlet,i} \), are specified such that the delivery \( D_{inlet,i} \) of the respective species (see Data Sheet 1 in Supplementary Material for calculation) matches the delivery at the outlet of the previous level:

\[
D_{inlet,i} = D_{outlet,i+1} \quad \text{for arteries,}
\]

\[
D_{inlet,v,i} = D_{outlet,v,i-1} \quad \text{for veins. (21)}
\]

The venous return \( P_{O_2,inlet,v,0} \) is specified such that:

\[
D_{O_2,inlet,v,0} = D_{O_2,outlet,a,0} + \dot{V}_{O_2,M} - J_{O_2,c}. \quad (22)
\]

where \( \dot{V}_{O_2,M} \) and \( J_{O_2,c} \) are the medullary oxygen consumption rate and the flux of oxygen between the capillaries and the cortical tissue, respectively.

To set the boundary conditions on the venous return for carbon dioxide transport, we consider the \( CO_2 \) transport dynamics in the vicinity of a proximal tubular cell as shown in Figure 2. Here we assume that all cortical \( CO_2 \) production is due to active transport by the tubules, as the contribution of basal metabolism is small [3–18% in the mammalian kidney (Cohen and Kamm, 1981)]. We therefore further assume that all of the \( CO_2 \) produced in the cortex is taken up by the nearby capillaries and transported to the venous return (thus does not diffuse into arterioles in the vicinity), where \( CO_2 \) produced in the medulla is added as well. The bicarbonate generation

---

**Table 3** | Renal artery inlet boundary condition values.

| Parameter | Value  | References |
|-----------|--------|------------|
| \( P_{CO_2} \) | 40 mmHg | Dash et al., 2016 |
| \( pH_{H^+}^{RBC} \) | 7.24 | Dash et al., 2016 |
| \( C_{HCO_3^-}^{RBC} \) | 6.52 mM | Present study |
| \( C_{HCO_3^-} \) | 26.37 mM | Present study |
| \( pH \) | 7.4 | Dash et al., 2016 |
| \( C_{CO_2}^{P} \) | 24.72 mM | Present study |
| \( C_{Cl^-}^{P} \) | 100 mM | Present study |
| \( P_{O_2} \) | 79 mmHg | Welch et al., 2001 |

\( P_{CO_2} \), carbon dioxide partial pressure; \( P_{O_2} \), oxygen partial pressure; \( pH_{H^+}^{RBC} \), pH in RBC; \( pH \), pH in plasma; \( C_{HCO_3^-}^{RBC} \), bicarbonate ion concentration in RBC; \( C_{HCO_3^-} \), chloride ion concentration in RBC; \( C_{CO_2}^{P} \), bicarbonate ion concentration in plasma; \( C_{Cl^-}^{P} \), chloride ion concentration in plasma. \( C_{HCO_3^-}^{P} \) and \( C_{Cl^-}^{P} \) are calculated from chemical equilibrium with \( P_{CO_2} = 40 \) mmHg, \( pH_{H^+}^{RBC} = 7.24 \) and \( pH = 7.4 \). \( C_{CO_2}^{P} \) is set to a standard value and \( C_{Cl^-}^{P} \) is specified such that \( J_{HCO_3^-} = 0 \), i.e., \( \frac{C_{HCO_3^-}}{C_{Cl^-}} = \frac{C_{CO_2}^{P}}{C_{Cl^-}^{P}} \). The exact values of \( C_{HCO_3^-} \) and \( C_{Cl^-}^{P} \) are not important, but their ratio is, as it determines the driving force for transmembrane transport. Chloride ions are not involved in any other reaction but the exchange of chloride with bicarbonate ions over the RBC membrane (Huang, 1991).
rate required to preserve acid-base homeostasis of the blood is approximately 1 mmol/kg body weight (Boron and Boulpaep, 2012), or 0.19 μmol/min for a Wistar Kyoto (WKY) rat. We neglect this bicarbonate generation, as its rate is much smaller than the overall carbon dioxide production rate (see Table 4). CO₂ produced by the proximal tubular cell is transported into the nearby capillaries in both CO₂ and bicarbonate form, for which the ratio is unknown. Their ratio on the venous return is also unknown since they are subject to further reactions on the path from the capillaries to the venous return. We therefore consider two extreme conditions on the venous return and assume that the real state lies somewhere between these two conditions (see Data Sheet 1 in Supplementary Material for details):

**Condition 1**: Balanced CO₂ distribution on the venous return. This condition assumes that the total renal CO₂ production is distributed into all forms of CO₂ on venous return, i.e., CO₂ in plasma and RBC, HCO₃⁻ in plasma and RBC, and hemoglobin bound CO₂.

**Condition 2**: Unbalanced CO₂ distribution on the venous return. This condition assumes that the total renal CO₂ production is distributed into all forms of CO₂ except HCO₃⁻ in plasma on venous return.

The above given BCs ensure for both conditions that total oxygen and carbon dioxide delivery throughout the kidney is conserved, i.e., \( D_{CO_2, inlet,a,10} = D_{CO_2, outlet,v,10} - V_{O_2,C} - V_{O_2,M} \) and \( D_{CO_2,T, inlet,a,10} = D_{CO_2,T, outlet,v,10} - V_{CO_2,C} - V_{CO_2,M} \) (see Figure 3). \( D_{CO_2,T} \) is the total carbon dioxide delivery, which is the sum of deliveries of CO₂ in plasma and RBC, hemoglobin-bound CO₂ and HCO₃⁻ in plasma and RBC (see Data Sheet 1 in Supplementary Material for calculation).

As to the outlet BCs, convective flux boundary conditions are imposed on all vessel outlets by setting the diffusive flux to zero. On all lateral surfaces, diffusive flux is set to zero. At the vessel-tissue interfaces, there is continuity of oxygen and carbon dioxide partial pressure and oxygen and carbon dioxide flux such that:

\[
\alpha^P_{O_2} D^P_{O_2} \frac{\partial P_{O_2}}{\partial r} = \alpha^T_{O_2} D^T_{O_2} \frac{\partial P_{O_2}}{\partial r}, \quad r = R. \quad (23a)
\]

**Base Case**

The base case is derived from in vivo \( P_{O_2} \) measurements with oxygen-sensitive ultramicroelectrodes in normotensive WKY rats as reported by Welch et al. (2001). Relevant values for

**TABLE 4 | Base case values.**

| Value          | Base case       | References     |
|----------------|-----------------|----------------|
| \( P_{O_2, RA} \) | 79 mmHg         | Welch et al., 2001 |
| \( P_{CO_2, RA} \) | 40 mmHg         | Dash et al., 2016 |
| \( \rho_P, RA \) | 7.4             | Dash et al., 2016 |
| \( \rho_H, RA \)  | 7.24            | Dash et al., 2016 |
| RBF            | 5.61 mL/min     | Welch et al., 2001 |
| \( D_{O_2, RA} \) | 46.09 μmol/min  | Welch et al., 2001 |
| \( D_{CO_2,T, RA} \) | 109.79 μmol/min | Present study   |
| \( V_{O_2} \)   | \(-8.36 \mu mol/min\) | Welch et al., 2001 |
| \( V_{CO_2} \)   | 6.69 μmol/min   | Present study   |

\( P_{O_2, RA} \), \( P_{CO_2, RA} \), \( \rho_P, RA \), \( \rho_H, RA \), RBF, \( D_{O_2, RA} \), \( D_{CO_2,T, RA} \), \( V_{O_2} \), \( V_{CO_2} \), \( \rho_P, RA \), \( \rho_H, RA \), RBF, renal artery oxygen delivery; \( D_{CO_2,T, RA} \), renal artery total carbon dioxide delivery; \( V_{O_2} \), oxygen consumption rate; \( V_{CO_2} \), carbon dioxide production rate.

\( \alpha^P_{O_2} D^P_{O_2} \frac{\partial P_{O_2}}{\partial r} = \alpha^T_{O_2} D^T_{O_2} \frac{\partial P_{O_2}}{\partial r}, \quad r = R. \quad (23b) \)
the base case are summarized in Table 4. Of these, renal blood flow (RBF), oxygen delivery (DO2), oxygen consumption rate (VO2) and renal artery POCO (PO2,RA) are measured values (Welch et al., 2001), renal artery POCO (PO2,RA), pHRBC,RA and pHP,RA are based on systemic arterial blood (Dash et al., 2016), and carbon dioxide delivery (DCO2) is calculated based on these values and the rest of the renal artery inlet boundary conditions presented in Table 3. To set the carbon dioxide production rate in dependence of the oxygen consumption rate, we assume a respiratory quotient (RQ) of 0.8 (Weidemann and Krebs, 1969; Burke et al., 1999; Dash and Bassingthwaighte, 2006). Prescribing the reference renal artery PO2, PO2,RA, on the renal artery inlet, the total heme group concentration is set such that the renal artery oxygen delivery (DO2,inlet,a,10) matches the values given in Table 4. Hence, the total heme group concentration is set to CO2HBT = 19.01 mol/m3 for the base case. We set capillary PO2, PO2,c, to an average of afferent arteriole outlet and venous return inlet, i.e., PO2,c = 0.5(PO2,outlet,a,8 + PO2,inlet,v,9). See Olgac and Kurtcuoglu (2015a) for details on capillary PO2.

RESULTS

Base Case under Conditions 1 and 2

We first present the output of the model employing two different boundary conditions on the venous return. Condition 1 distributes total renal CO2 production into all forms of CO2 in the venous return, whereas Condition 2 excludes plasma bicarbonate in this distribution. Figures 4A,B demonstrate on the left panel under Condition 1 and on the right panel under Condition 2, arterial, venous and tissue POCO as well as plasma and RBC pH profiles, respectively. Condition 1 results in flatter profiles of both POCO and pH compared to Condition 2. Under Condition 1, POCO increases from 40 mmHg at the inlet of the renal artery (order 10) to 40.8 mmHg at the outlet of the afferent arteriole (order 0). Under Condition 2, the increase is to 42.3 mmHg. On the venous return, under Condition 1, POCO = 43.5 mmHg, whereas under Condition 2, POCO = 52.8 mmHg. The lower increase in POCO under Condition 1 is due to the fact that CO2 production is distributed into all forms of CO2 on the venous return, including the dominant plasma bicarbonate. Conversely, as there is no plasma bicarbonate added to the venous return under Condition 2, the same rate of renal CO2 production results in a higher increase in POCO. This is also evident in the pH profiles: Under Condition 1, the pH profiles are almost flat with a slight overall decrease in plasma and RBC pH on the venous side due to the increased acidity (added renal CO2 production). Under Condition 2, plasma and RBC pH on the venous return are 7.28 and 7.21, respectively. This increased acidity is again owed to the addition of produced CO2 to the venous return in forms other than plasma bicarbonate. Figure 4C shows for both conditions the flux of carbon dioxide between artery walls and the tissue. As indicated by the negative fluxes, there is venous-to-arterial carbon dioxide shunting under both conditions, with more shunting under Condition 2. Overall, approximately 0.5 and 1.4% of the total renal carbon dioxide delivery is shunted under Conditions 1 & 2, respectively. The larger amount of carbon dioxide shunting under Condition 2 is primarily due to the higher POCO gradient between the venous and the arterial sides compared to Condition 1.

The investigated Conditions 1 and 2, i.e., the distribution of total renal CO2 in all forms of CO2 on the venous return and the exclusion of plasma bicarbonate during this distribution, respectively, represent extreme cases. The real state must lie between these two. We therefore estimate the average cortical POCO, POCO,c, to be between 42.0 and 46.0 mmHg.

Effects Of CO2 Transport on O2 Shunting

We performed O2 transport calculations with a constant P50 and a variable P50 whose dependence on the local POCO and pH is given by Equation 6(a)–(c). The O2 transport calculations with variable P50 are based on the POCO and pH fields obtained from carbon dioxide transport calculations under Condition 2, because under this condition, the maximum possible increase in POCO and decrease in pH in the preglomerular vasculature compared to the systemic arterial blood are reached. In other words, this condition captures the highest possible effect of CO2 transport on O2 transport.

Figures 5A,B show PO2 profiles in arteries, veins and tissue, as well as oxygen fluxes between vein walls and tissue. The PO2 profiles for the constant and variable P50 cases are very similar, with a slight overall increase in PO2 for the variable P50 case due to higher P50 compared to the constant P50 case. For the constant P50 case, cumulatively 0.6% of the total renal oxygen delivery is shunted from the arteries to the veins along wrapped artery-vein pairs, whereas 0.2% of the total renal oxygen delivery is supplied to the tissue by the veins along not-wrapped artery-vein pairs. Hence, for this case, the total preglomerular AV oxygen shunting is 0.4% of the total renal oxygen delivery. Note that these results are slightly different from the ones given in our previous study (Olgac and Kurtcuoglu, 2015b). This is due to the fact that we used P50 = 34 mmHg there compared to P50 = 26.8 mmHg in the current study.

Under variable P50 conditions, oxygen shunting along the wrapped vessels decreases, with overall preglomerular AV oxygen shunting reducing to 0.15% of the total renal oxygen delivery. Hence, CO2 effects do not promote but rather decrease preglomerular AV O2 shunting. This is because the increase in acidity (and hence the decrease in the affinity of hemoglobin to oxygen) is more pronounced on the venous compared to the arterial side.

Effects of Buffering Capacity

To test the influence of buffering capacity, we performed calculations on a modified base case with a 10 fold decrease in plasma and RBC buffering capacities. Figures 6A–C represent, on the left panel under Condition 1 and on the right panel under Condition 2, POCO, pH and carbon dioxide flux profiles for this modified case. Compared to the base case results presented in Figure 4, under both Conditions 1 & 2, the increase in POCO and decrease in pH are more pronounced when the buffering capacity is decreased. POCO increases to 42.8 and 46.2 mmHg at the outlet of the afferent arteriole (order 0) under Conditions 1 & 2, respectively. On the venous return, under Condition 1, POCO = 49.1 mmHg, whereas under Condition 2, POCO = 63.2 mmHg.
Furthermore, pH profiles vary more compared to the rather flat profiles in Figure 4. On the venous return, plasma and RBC pH are 7.30 and 7.18, respectively, under Condition 1, compared to 7.20 and 7.10, respectively, under Condition 2. VA CO₂ shunting is also increased due to the increased \( P_{\text{CO}_2} \) gradient between the venous and the arterial side, with 1.2 and 2.4% of the total renal CO₂ delivery shunted from the preglomerular veins to the arteries under Conditions 1 & 2, respectively.

DISCUSSION

We have made the following key observations:

1. Increase in acidity in the preglomerular vasculature compared to systemic arterial blood is marginal. 2 \( \text{CO}_2 \) effects do not promote preglomerular arterial-to-venous O₂ shunting but rather impair it. In the following we will discuss these observations.

Marginal Increase in Acidity in the Preglomerular Vasculature

We calculated the \( P_{\text{CO}_2} \) at the outlet of the afferent arteriole and on the venous return to be in the range of 40.8–42.3 mmHg and 43.5–52.8 mmHg, respectively, for a renal arterial \( P_{\text{CO}_2} \) of 40 mmHg. Plasma and RBC pH on the venous return decrease to somewhere between 7.28–7.39 and 7.21–7.23, respectively, compared to their systemic arterial values of 7.4 and 7.24, respectively. Taken together, we conclude that the increase in
acidity in the preglomerular vasculature is not substantial. The main reason for this is the high buffering capacity of blood. When we lowered the buffering capacity in our model, acidity increased substantially. It should be noted that there may be more pronounced increase in acidity in the postglomerular vasculature, along the peritubular capillary network and/or the vasa recta. Our current model does not include these parts.

Previous modeling studies by Bidani et al. (1984) and Atherton et al. (1988) were based on the proximal tubular PCO₂ of 65 mmHg measured by DuBose et al. (1979). They indicated that substantial venous-to-arterial CO₂ shunting would be necessary to preserve this PCO₂ of 65 mmHg in the renal cortex. Here we calculated average cortical PCO₂, PCO₂,C, to be between 42.0 and 46.0 mmHg. We further calculated the shunting of CO₂ from the veins to the arteries to be approximately between 0.5 and 1.4% of the total renal carbon dioxide delivery. We conclude that just as the increase in acidity, the venous-to-arterial CO₂ shunting in the preglomerular vasculature is also only marginal.

**CO₂ Effects Impair Preglomerular AV O₂ Shunting**

We observed that when calculations are based on a variable P₅₀ that is dependent on the local PCO₂ and pH, the AV O₂ shunting decreases. This is mainly because the increase in acidity is higher on the venous side, which leads to a lower affinity of hemoglobin to oxygen compared to the arterial side. This lower affinity on the venous side makes it slightly harder for the oxygen to bind to hemoglobin, diminishing the oxygen transfer from the tissue into the veins, hence decreasing AV O₂ shunting. Therefore, our model does not support the hypothesis initially proposed by Schurek et al. (1990) that renal CO₂ trapping through a reverse CO₂ shunting mechanism may enhance AV O₂ shunting through the Bohr effect. The current model thus also confirms our previous findings that preglomerular AV O₂ shunting is marginal, and that if substantial renal oxygen shunting exists, it should be along the post-glomerular vasculature, i.e., the peritubular capillary network and/or the vasa recta (Olgac and Kurtcuoglu, 2015a,b).

**Limitations of the Model**

The main limitation of the model is that the distribution of the different forms of CO₂ in the venous return is unknown. To address this, two different conditions representing extreme cases were employed and ranges of values reported. The actual values representing the real state are expected to lie within the given ranges. More accurate calculations would require that CO₂ transport dynamics in the peritubular capillary network be taken into account, which would necessitate explicit treatment of the
postglomerular vasculature and the tubular system. Modeling bicarbonate reabsorption in this domain would yield an estimate of what fraction of the carbon dioxide produced in the tubular cells reaches the capillaries in bicarbonate and CO$_2$ form, respectively. This fraction is unknown in the current model. Nevertheless, the two conditions employed on the venous return provide solid boundaries for the ranges of P$_{CO_2}$ and pH in the preglomerular vasculature, and the conclusions reached in this study are valid for both conditions.

A further limitation of this computational study is produced by the fact that there are no comparable experimental studies of renal carbon dioxide transport which could be used for validation. The experimental P$_{CO_2}$ and pH measurements referred to in the Introduction section have been performed on tubules and stellate vessels, and can thus not be compared with our results. Quantitative cortical tissue and afferent arteriole P$_{CO_2}$ and pH values have, to our knowledge, not been published. To test the robustness of our conclusions, we performed sensitivity analyses in which we altered renal artery inlet boundary conditions.

First, we established alternative chemical equilibria at the renal artery inlet corresponding to renal artery P$_{CO_2}$ values of 35 mmHg and 45 mmHg, respectively. This accounts for possible variation in renal artery P$_{CO_2}$ in the physiologic range. We calculated maximum P$_{CO_2}$ at the outlet of the afferent arteriole and on the venous return to be 37.1 and 47.1 mmHg, respectively,
for renal artery P\textsubscript{CO\textsubscript{2}} of 35 mmHg, and 47.6 and 58.5 mmHg, respectively, for renal artery P\textsubscript{CO\textsubscript{2}} of 45 mmHg (Supplementary Figure 1, Supplementary Table 1). These extreme cases show relative increases in P\textsubscript{CO\textsubscript{2}} in the preglomerular vasculature with respect to renal artery P\textsubscript{CO\textsubscript{2}} that are similar to the base case. Plasma and RBC pH on the venous return decrease to minima of 7.32 and 7.22, respectively, for renal artery P\textsubscript{CO\textsubscript{2}}, 35 mmHg, plasma pH of 7.45 and RBC pH of 7.25 (Supplementary Figure 1, Supplementary Table 1). For the other extreme case with renal artery P\textsubscript{CO\textsubscript{2}} of 45 mmHg, plasma pH of 7.35 and RBC pH of 7.23, we calculated minimum plasma and RBC pH on the venous return to be 7.24 and 7.20, respectively (Supplementary Figure 1, Supplementary Table 1). These relative decreases in pH in the preglomerular vasculature with respect to renal artery pH in the extreme cases are similar to that in the base case. Furthermore, oxygen transport calculations in these extreme cases under variable P\textsubscript{50} conditions show impaired AV oxygen shunting compared to under constant P\textsubscript{50} conditions, just as it was observed in the base case (Supplementary Figures 2, 3). There, under variable P\textsubscript{50} conditions, overall preglomerular oxygen shunting reduced to 0.15% of the total renal oxygen delivery, compared to 0.40% under constant P\textsubscript{50} conditions. In the extreme cases, this reduction was to 0.20 and 0.10% of the total renal oxygen delivery for renal arterial P\textsubscript{CO\textsubscript{2}} of 35 mmHg and 45 mmHg, respectively (Supplementary Table 2).

In a second analysis, we altered the renal blood flow rate (RBF) by 30% in either direction. With a 30% decrease in RBF, the increase in acidity in the preglomerular vasculature became more pronounced. We calculated for this case maximum P\textsubscript{CO\textsubscript{2}} at the outlet of the afferent arteriole and on the venous return to be 44.1 and 59.6 mmHg, respectively (Supplementary Figure 4, Supplementary Table 3). Plasma and RBC pH on the venous return decrease to minima of 7.23 and 7.20, respectively. Conversely, with a 30% increase in RBF, the increase in acidity in the preglomerular vasculature became less pronounced with maximum P\textsubscript{CO\textsubscript{2}} of 41.6 and 49.5 mmHg at the outlet of the afferent arteriole and on the venous return, respectively, and minimum plasma and RBC pH on the venous return of 7.31 and 7.22, respectively (Supplementary Figure 4, Supplementary Table 3). In these extreme cases, AV O\textsubscript{2} shunting reduced from 0.81% (under constant P\textsubscript{50} conditions) to 0.32% (under variable P\textsubscript{50} conditions) of the total renal oxygen delivery (with 30% decrease in RBF) and from 0.21% (under constant P\textsubscript{50} conditions) to 0.05% (under variable P\textsubscript{50} conditions) of the total renal oxygen delivery (with 30% increase in RBF) (Supplementary Figures 5, 6, Supplementary Table 4). In comparison, in the base case, AV O\textsubscript{2} shunting reduced from 0.40% (under constant P\textsubscript{50} conditions) to 0.15% (under variable P\textsubscript{50} conditions) of the total renal oxygen delivery (Supplementary Table 4).

We conclude that our first main observation, namely that increase in acidity in the preglomerular vasculature compared to systemic arterial blood is marginal, is robust unless RBF is substantially reduced. Our second main observation, i.e., that CO\textsubscript{2} effects do not promote preglomerular arterial-to-venous O\textsubscript{2} shunting but rather impairs preglomerular arterial-to-venous oxygen shunting.

CONCLUSIONS

Our model suggests that under normal physiologic conditions, the increase in acidity in the preglomerular vasculature compared to systemic arterial blood is marginal, and that venous-to-arterial shunting of carbon dioxide does not promote, but rather impairs preglomerular arterial-to-venous oxygen shunting.

AUTHOR CONTRIBUTIONS

UO and VK designed this research; UO and VK developed the mathematical model; UO implemented the computational model and performed the computations; UO and VK interpreted results of the computations; UO prepared figures; UO drafted the manuscript; UO and VK edited and revised the manuscript; UO and VK approved final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphys.2016.00482/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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NOMENCLATURE

AV Arterial-to-venous
A Carbonic anhydrase activity factor
BC Boundary condition
C Concentration
DP Diffusion coefficient in plasma
DT Diffusion coefficient in tissue
D Delivery
DPG 2,3-Diphosphoglycerate
e Relative error
f Water fraction of total RBC volume
h(r) Radial hematocrit profile
Hc Capillary hematocrit
J Flux
K Permeability
KA Equilibrium association rate constant
K Apparent dissociation constant for H2CO3
K1 First dissociation constant for H2CO3
KDPG Association constant for DPG and hemoglobin
k Number of vessels
ktrans Translocation rate constant
ku CO2 hydration reaction rate
kv H2CO3 dehydration rate constant
l Length of vessel
LS Lumen separation
M Local consumption/production rate
Mc Capillary source/sink
NA Avogadro number
n Empirical constant in Hill equation
P50 Half saturation oxygen partial pressure
P Partial pressure
r Radial location
R Reaction rate
Ra Artery radius
Rv Vein radius
RBC Red blood cell
RRC Radius of RBC disk
RBF Renal blood flow rate
RQ Respiratory quotiend
SO2 Saturation of hemoglobin with oxygen
tRBC Maximum half thickness of RBC
Ttot Total number of anion transporters on RBC membrane
u Oxygen advection velocity in capillaries
u(r) Radial velocity profile in RBC-rich region
u'(r) Radial velocity profile in RBC-free region
V Consumption/production rate
VA Venous-to-arterial
WKY Wistar Kyoto rat
z Axial location
α Solubility coefficient
β Buffering capacity
δ Thickness of RBC-free region
λα Association constant for CO2 binding to the α-chain of hemoglobin
λβ Association constant for CO2 binding to the β-chain of hemoglobin
φ Fractional capillary volume

Superscripts and subscripts

a Arterial
AT Anion transporter
c Capillary
C Cortical
Cl Chloride ion
CO2 Carbon dioxide
H+ Hydrogen ion
HbO2 Heme groups bound to oxygen
HbCO2 Hemoglobin carbamate
HbCO2,T Total hemoglobin bound CO2
O2HbCO2 Oxyhemoglobin carbamate
HbT Total heme groups
HCO3 Bicarbonate ion
i Representative level
M Medullary
nw Not-wrapped
O2 Oxygen
P Plasma
RA Renal artery
RBC Red blood cell
S Standard physiological
T Tissue
v Venous
w wrapped