Reply to “Letter to the editor: ‘The plausibility of arterial-to-venous oxygen shunting in the kidney: it all depends on radial geometry’”

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REPLY: We thank Evans and coworkers for their attention to our work, which is inspired by their studies on oxygen transport dynamics (2, 3, 6). In their letter (1), Evans et al. bring forth two main points of criticism of our article (8): first, that there should be diffusive oxygen shunting between arteries and veins in the renal cortex, and, second, that wrapping of veins around arteries may induce considerable pre-glomerular arterial-to-venous (AV) oxygen shunting. We agree with the first statement, but point out that it does not contradict the results of our study. We do not agree with the second. Here are our responses to each point.

With regard to point 1, we agree with Evans et al. (1) that “the experimental findings of Levy and colleagues can only be satisfactorily explained by diffusive shunting of oxygen between arteries and veins in the renal cortex.” In the study that Evans et al. refer to, Levy and Imperial (4) studied the superficial and the deeper regions of the kidney independently, observing in both cases that oxygen had on average a shorter transit time through the kidney than erythrocytes. They concluded that “shunting of oxygen occurs in both the renal cortex and medulla, but the degree to which it occurs in each zone cannot be quantified from the present data.” Indeed, the results of Levy and Imperial can be considered proof of renal oxygen shunting. However, one cannot infer from their data the main location or locations of shunting within the cortex and medulla, and one cannot conclude that shunting constitutes a substantial portion of oxygen delivery to the kidney. In our study (8), we investigated pre-glomerular oxygen transport dynamics and concluded that significant AV oxygen shunting is unlikely to occur in the pre-glomerular vasculature. This does not exclude the possibility of substantial oxygen shunting in both the renal cortex and the medulla. If present, such shunting would likely occur in locations with favorable anatomic arrangements, namely, between the arterial portion and the venous end of the cortical peritubular capillary bed (4, 5).

With regard to point 2, Evans and coworkers suggested that the pre-glomerular vasculature should also be considered as a potential location for substantial oxygen shunting, since it features wrapped artery-vein pairs (1, 6). These offer relatively short diffusion distances without the presence of major oxygen sinks, which are favorable conditions for oxygen shunting. In their letter (1), Evans et al. propose that we modify our computational model to quantify the contribution of wrapped artery-vein pairs, which we had taken into account implicitly but not explicitly. We have repeated the calculations for the WKY base case presented (8) accordingly, building on the latest dataset published by Evans and colleagues (6). Instead of using a lumped average diffusion distance for the wrapped and not-wrapped artery-vein pairs (8), we separated the computational domain into two subdomains: one

Table 1. Structural information and tissue oxygen consumption values at representative levels

<table>
<thead>
<tr>
<th>Level</th>
<th>knw</th>
<th>kw</th>
<th>LS nw, LSw, ( \mu m )</th>
<th>Mnw, mol·s(^{-1})·m(^{-3} )</th>
<th>Mw, mol·s(^{-1})·m(^{-3} )</th>
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<tbody>
<tr>
<td>0</td>
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<td>11.2</td>
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<td>1</td>
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<td>12,804</td>
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<td>10.6</td>
<td>−0.0610</td>
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<tr>
<td>2</td>
<td>5,537</td>
<td>3,879</td>
<td>112.7</td>
<td>10.6</td>
<td>−0.0291</td>
</tr>
<tr>
<td>3</td>
<td>1,700</td>
<td>1,226</td>
<td>112.7</td>
<td>10.6</td>
<td>−0.0291</td>
</tr>
<tr>
<td>4</td>
<td>288</td>
<td>922</td>
<td>86.1</td>
<td>11.7</td>
<td>−0.0312</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>319</td>
<td>86.1</td>
<td>11.7</td>
<td>−0.0312</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>121</td>
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<td>−0.0250</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>33</td>
<td>86.6</td>
<td>17.9</td>
<td>−0.0250</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>8</td>
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<td>17.9</td>
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<td>1</td>
<td>86.6</td>
<td>37.0</td>
<td>−0.0138</td>
</tr>
</tbody>
</table>

k, no. of vessels; LS, lumen separation; M, local oxygen consumption rate; nw, not-wrapped vessels; w, wrapped vessels. LS values are derived from Fig. 8 in Ref. 6 based on arterial caliber with the exception of order 10. LS for order 10 is considered larger than reported in Ref. 6 to avoid overlap of veins in the computational domain (see Fig. 1 in Ref. 8). This LS value is still smaller than LS and only affects one single artery-vein pair. All LS values read from Fig. 8 in Ref. 6 are multiplied by a factor of 0.94 to match the cortex volume of 0.98 cm\(^3\) based on \( \mu \)CT data (8) (for details on the cortical volume calculation, refer to the APPENDIX in Ref. 8). The total number of vessels, \( k = k_{nw} + k_{kw} \), is taken from Nordsletten et al. (7). We used the same data in our original study (8). The proportion of wrapped to not-wrapped vessels on each order is based on Fig. 8 in Ref. 6.

Fig. 1. Oxygen flux across vein walls, \( J_{O_2,v} \), for the WKY base case with wrapping explicitly included: comparison between wrapped and not-wrapped vessels. All results are reported as percentage of total renal oxygen delivery, \( D_{O_2,RA} \). Cumulative values as well as values for each individual order are shown. Positive flux represents flux from the vessel into the tissue, whereas negative flux denotes the opposite; i.e., negative \( J_{O_2,v} \) denotes oxygen shunted to the venous tree.

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contained the wrapped, the other the not-wrapped vascular segments, allowing us to include the effect of wrapping in an explicit manner. The number of vessels (k) and lumen separation (LS) distances for the wrapped and not-wrapped segments derived from Fig. 8 in Ref. 6 and used in our new calculations are given in Table 1. Since the tissue between the wrapped artery-vein pairs is free of capillaries and tubules (6), we set, for the wrapped subdomain, both the tissue oxygen consumption and fractional capillary volume to zero. The latter implies that oxygen only diffuses between the artery and the wrapping vein but is not advected along capillaries.

Figure 1 shows the calculated oxygen flux across the vein walls ($J_{O_2,v}$) for the WKY base case in which wrapping is explicitly included. We see that 0.51% of the total renal oxygen delivery diffuses from the arterial to the venous side along wrapped vessels, whereas 0.38% of the total renal oxygen delivery is supplied to the tissue from the veins along the not-wrapped vessels. This means that, overall, only 0.13% of the total renal oxygen delivery is shunted from pre-glomerular arteries to veins.

To obtain an estimate of AV oxygen shunting that is independent of our model, we considered the oxygen fluxes between artery-vein pairs as determined by Evans and colleagues using a two-dimensional computational model (6). In Fig. 1A in Ref. 6, AV oxygen fluxes are reported to be 19.0 and 43.9 nmol·m$^{-1}$·min$^{-1}$ for small (25-μm diameter) and large (89 μm) wrapped arteries, respectively. The corresponding AV fluxes in not-wrapped vessel pairs are null. One can estimate, from Fig. 8 in the same article, that 25.9% of small arteries (<50-μm diameter) and 78.0% of large arteries (> 50 μm) are wrapped. Using the structural data of Nordsletten et al. (7), which we also utilized in our model (Table 1 in Ref. 8), the total lengths of the pre-glomerular small and large arteries can be determined to be 22.95 and 1.73 m, respectively. Multiplying the reported fluxes with the total lengths of arteries and the percentages of wrapped pairs for the small and large arteries, one obtains a total pre-glomerular AV shunting rate of 0.17 μmol/min, which is 0.37% of the total renal oxygen delivery for the WKY base case.

In conclusion, neither our own calculations in which we have taken into account wrapped artery-vein pairs explicitly, nor the flux estimates based on the calculations of Evans and colleagues, suggest any noteworthy pre-glomerular AV oxygen shunting. Two main reasons for this have been stated by Evans et al. in their letter (1): 1) “the presence of oxygen sinks of any kind between an artery-vein pair should prevent AV oxygen shunting”; and 2) “The phenomenon of wrapping is particularly prominent in larger vessels (≥ 50 μm in diameter).” The former limits AV shunting to wrapped pairs, whereas the latter states that wrapping occurs predominantly in larger vessels, together leading to negligible pre-glomerular AV shunting.

All that said, we agree with Evans et al. (1) that “the jury must remain out on the question of whether AV oxygen shunting is an important phenomenon in the regulation of intrarenal oxygenation.” Data on post-glomerular oxygen shunting along the peritubular capillary network and the vasa recta would be of particularly high value for finding an answer to that question.

GRANTS

The financial support of the Swiss National Center of Competence in Research on Control of Homeostasis by the Kidney (NCCR Kindey.CH) is kindly acknowledged.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: U.O. and V.K. provided conception and design of research; U.O. performed experiments; U.O. analyzed data; U.O. and V.K. interpreted results of experiments; U.O. prepared figures; U.O. drafted manuscript; U.O. and V.K. edited and revised manuscript; U.O. and V.K. approved final version of manuscript.

REFERENCES