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Purpose of review
Renal arteriovenous oxygen shunting has been proposed as a mechanism by which oxygen supplied to the kidney can bypass the renal parenchyma. Shunting could, therefore, play a crucial role in renal hypoxia and hyperoxia. In the absence of suitable quantitative experimental methods, computational modeling has been employed in recent years to estimate the extent and potential impact of oxygen shunting.

Recent findings
Overestimation of the separation distance between arteries and veins was suggested to be responsible for previous findings that only negligible amounts of oxygen are shunted in the preglomerular vasculature. However, models considering the correct separation distance and wrapping of artery–vein pairs still showed shunting at negligible levels of less than 1% of total renal oxygen delivery. The effect of reverse CO_2 shunting on the oxygen–hemoglobin dissociation curve was found to impair, rather than promote, preglomerular oxygen shunting.

Summary
Oxygen is unlikely to be shunted along the preglomerular vasculature in sufficient quantities to affect renal oxygenation. There may be substantial shunting at the level of the postglomerular vasculature, but more extensive efforts in structural imaging and computational modeling are needed to quantify it reliably.

Keywords
Bohr effect, carbon dioxide, computational modeling, oxygen shunting, renal oxygenation

INTRODUCTION

The existence of renal arteriovenous oxygen shunting was first demonstrated by Levy and Sauceda [1], proposing it as an answer to why the ratio of blood oxygen concentration between the renal artery and renal vein stays largely constant over a wide range of blood flow rates [2].

This phenomenon had been observed in several independent studies at the time. Its presumed cause was the inability of the kidney to extract oxygen from blood to levels below the venous oxygen partial pressure. Although this would have been a reasonable explanation for a flow-limited organ in which the supply of oxygen is primarily restricted by the flow rate of the incoming blood, it was not for the kidney: the kidneys receive 20–25% of the cardiac output and are, therefore, supplied with oxygen well above what is necessary for their operation under normal conditions. Oxygen extraction should thus not be a limiting factor.

But what if oxygen could pass through the kidney without contributing to parenchymal oxygenation? Levy [2] proposed that oxygen may be shunted from arteries to veins, as these are arranged in part in countercurrent fashion, which could provide a shortcut to oxygen on its path from renal artery to renal vein. Levy and Sauceda [1] had previously found that oxygen can pass through the kidney more quickly than red blood cells by injecting highly oxygenated blood containing methemoglobin-labeled red blood cells into the renal artery in dogs: the rise in oxygen saturation at the renal vein occurred about a second before the first labeled erythrocytes arrived at the same location.

What Levy and Sauceda could not provide, however, was quantification of the amount of oxygen shunted. Yet this information is needed to assess whether a sufficient quantity of oxygen bypasses the parenchyma to render the kidney a flow-limited organ. It is also needed to evaluate the hypotheses that shunting prevents tissue hyperoxia by routing

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KEY POINTS

- Arteriovenous shunting has been proposed as a way for oxygen to bypass the renal parenchyma, possibly playing a crucial role in balancing renal oxygenation.
- To serve as an effective bypass, shunting would need to occur along the preglomerular vasculature, before the oxygen reaches the tubular cells, its main consumers.
- There is evidence for shunting, but there are currently no reliable experimental methods that can quantify the amount of oxygen bypass or the location of shunting.
- As an alternative, computational modeling has been used to calculate preglomerular oxygen shunting.
- The latest models indicate that only very small amounts of oxygen are shunted along the preglomerular vasculature.

excess oxygen quickly out of the kidney and that it exacerbates hypoxia when blood supply is reduced. Evans *et al.* [3] give an excellent overview of the experimental indications of oxygen shunting and their potential implication for kidney oxygenation and disease states. Kidney hypoxia may cause and aggravate acute kidney injury. Along with oxidative stress, it is associated with chronic kidney disease and may progress such toward renal failure.

As there are currently no experimental approaches for quantifying shunting, computational tools have been proposed to fill the gap. Such tools allow for the transformation of purely qualitative models to approximate quantitative ones, thereby enabling hypothesis testing. Concretely, we know that shunting depends on the anatomic arrangement of blood vessels, the permeability of vessel walls and surrounding tissue to oxygen, blood flow rate, oxygen consumption rate and local oxygen gradients, to name a few. What a computational model can do is to determine the combined effect of these factors and yield an estimate of the extent of oxygen shunting in different regions of the kidney under various physiological and pathophysiological conditions.

In the period covered by this review, Evans *et al.* [4▪] wrote a letter in reaction to a model of preglomerular oxygen shunting published by our research group [5▪], to which we responded in [6▪] and followed up with a further refined model in [7▪].

To provide the necessary context, our original model is comparable, conceptually, with the one published earlier by Gardiner *et al.* [8▪]. Both are based on a dataset by Nordsletten *et al.* [9], in which the renal vascular structure was derived from computed tomography (CT) images of rat kidneys acquired by Garcia-Sanz *et al.* [10], and ordered into hierarchical vessel segments separated by bifurcations. This Strahler ordering was performed for the preglomerular arteries and corresponding veins, yielding two separate vessel trees without the connecting smaller vessels due to the limited resolution of the original CT dataset. A schematic representation of such ordering is shown in Fig. 1a.

HIERARCHICAL ONE-DIMENSIONAL MODEL SUGGESTS THAT SHUNTING IS RELEVANT

The model of Gardiner *et al.* [8▪] relies on one-dimensional representations of those two ordered trees. Each hierarchical segment in the Nordsletten data is used as the basis of a computational compartment. In the individual compartments, a single artery and vein are arranged parallel to each other with opposing blood flow directions, using the average vessel diameter and length of the blood vessels of the corresponding Strahler order. Each compartment feeds blood to the next one, and blood exiting the artery in the final compartment is routed back through the corresponding vein after adjusting the blood partial pressure of oxygen (pO_2) for oxygen consumption in the tissue. This countercurrent system produces the pO_2 gradient required for arteriovenous oxygen shunting. The amount of O_2 transferred from the arterial to the venous segment in the respective compartment is considered proportional to that gradient and to the arterial vessel wall surface area.

To account for the effect of parameters that are not explicitly included in the model, a weighting factor is employed. This factor is determined by requiring that the calculated pO_2 in the renal tissue matches the values measured experimentally by Welch *et al.* [11].

The model output showed that approximately 10% of the total oxygen supplied to the kidney was shunted, which was comparable in magnitude with overall oxygen consumption. It further showed that shunting decreased with increased renal blood flow and hematocrit, and increased with elevated arterial pO_2. Therefore, Gardiner *et al.* concluded that shunting is a quantitatively significant factor in renal oxygen balance.

HIGHER DIMENSIONAL MODEL INDICATES NO SUBSTANTIAL SHUNTING

In the model by Olgac and Kurtcuoglu [5▪], the hierarchical structure of the computational compartments is retained, but each level of the vascular tree is represented by a repetitive, idealized three-

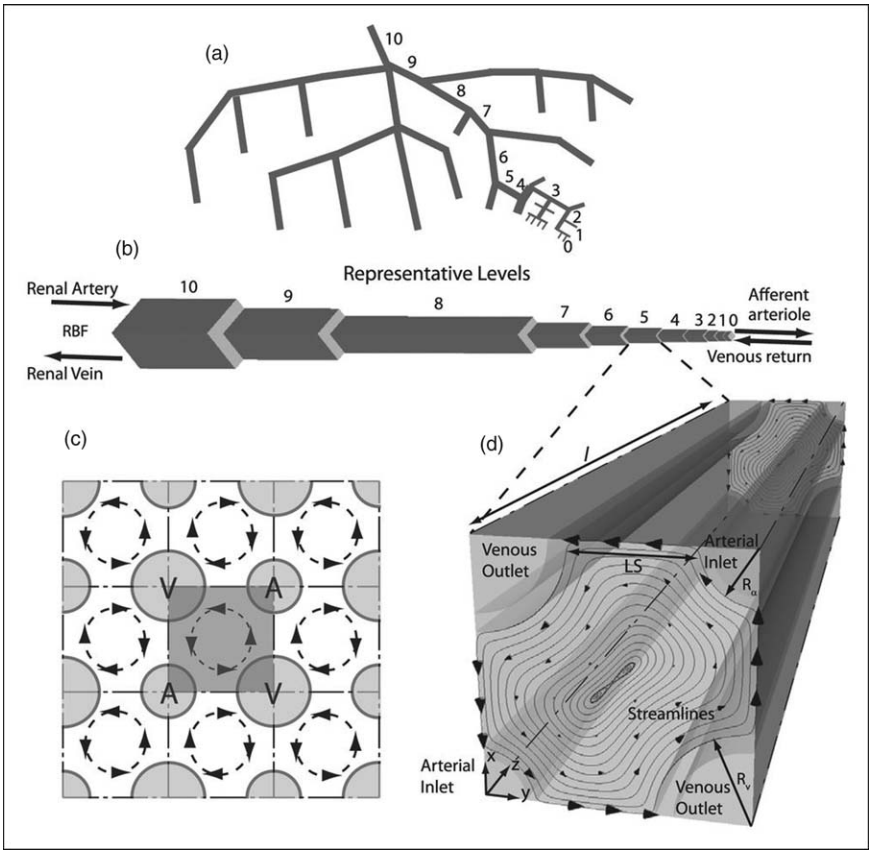

FIGURE 1. (a) Schematic representation of hierarchical ordering of blood vessels. The Strahler ordering begins at order 0 at the most distal part of the considered vessel tree, incrementing the order by 1 whenever vessels of the same order connect at a bifurcation, or retaining the order of the higher order vessel if vessels of different orders connect. (b) Computational compartments of the simulations of Olgac and Kurtcuoglu [5▪], here named representative levels. The model of Gardiner *et al.* [8▪] employs similar hierarchical compartments. (c) Geometric arrangement of the repetitive three-dimensional units at a given representative vessel level employed in [5▪]. (d) Geometric arrangement of vessels and tissue, as well as schematic representation of the effect of capillary blood flow on oxygen transport in a three-dimensional unit. Vessel lumen separation distances were calculated for each segment based on the histology data of Gardiner *et al.* [13]. Reproduced from [5▪].

dimensional domain (Fig. 1b, c and d). This domain contains artery–vein pairs with tissue in between and accounts for the effect of capillary blood flow on oxygen transport through tissue by employing the model of Salathé [12]. The blood vessels are not considered homogeneous one-dimensional entities, but the spatial distribution profile of red blood cells as well as the spatial variation of blood flow velocity in the vessel cross-sections are accounted for. Oxygen flux through the arterial and venous walls are calculated by modeling advection, diffusion and consumption in the three-dimensional domain of each hierarchical compartment. Compared with the model of Gardiner *et al.*, this model does not require weighting factors to match experimental data. It rather quantifies oxygen shunting by calculating the total oxygen flux across venous walls.

The model showed that under most of the considered conditions, the amount of oxygen shunted did not exceed consumption in the tissue, with tissue pO_2 staying below venous pO_2. Only when consumption was set to 0, notable shunting occurred, but even then it accounted for just 1.2% of the total oxygen delivered to the kidney. In that case, shunting was limited to the most distal vessels, similar to what was seen in the model of Gardiner *et al.*

LETTER TO THE EDITOR: THE MODEL GEOMETRY NEGLECTS VENOUS WRAPPING AROUND ARTERIES

Evans *et al.* [4▪] criticized the layout of the three-dimensional units employed by Olgac and Kurtcuoglu, stating that in the kidney larger preglomerular arteries and veins are arranged directly adjacent to each other, without capillaries or tubular tissue in between them (Fig. 2).

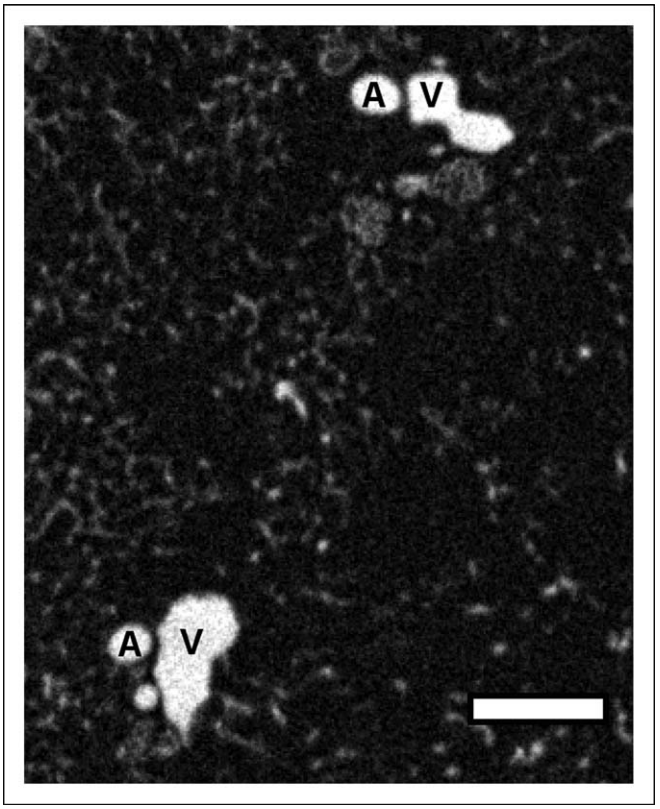

FIGURE 2. X-ray microcomputed tomography scan of a mouse kidney vascular cast showing the relative localization of preglomerular arteries (A) and veins (V) at the corticomedullary border. Scale bar: 200 μm.

Gardiner *et al.* [13] and later Ngo *et al.* [14] had previously created a two-dimensional model based on histology images, using idealized and realistic vessel geometries, respectively. In the second model, arteries, veins, tubules and capillaries were extracted from histology images and used to calculate oxygen diffusion and consumption in the two-dimensional space of the pictures. It was found that in vessel pairs, in which the vein partially wrapped around the artery, substantial arteriovenous oxygen shunting occurred, whereas in nonwrapped pairs most of the oxygen was delivered to the tissue. Evans *et al.* concluded that Olgac and Kurtcuoglu did not find oxygen shunting because their model neglected vessel wrapping.

REPLY TO THE LETTER: MODEL WITH FULL ACCOUNT OF WRAPPED VESSELS INDICATES NEGLIGIBLE SHUNTING

In response, Olgac and Kurtcuoglu revised the model to treat wrapped and nonwrapped vessels separately. In addition, they extrapolated the two-dimensional model of Ngo *et al.* to the third dimension by multiplying over the total length of the corresponding blood vessels. Calculations with both showed negligible oxygen shunting, namely 0.13 and 0.37% of the total oxygen delivery, respectively. Wrapping occurs predominantly in large vessel pairs, which make up only a small part of the total vascular surface area. Consequently, although there can be shunting in these pairs, there are not enough of them to shunt substantial amounts of oxygen.

MODEL ACCOUNTING FOR CARBON DIOXIDE TRANSPORT ALSO SHOWS NEGLIGIBLE OXYGEN SHUNTING

Schurek *et al.* [15] had hypothesized earlier that carbon dioxide may be shunted from veins to arteries, thereby promoting dissociation of oxygen from hemoglobin through the Bohr effect and thus contributing to oxygen shunting. To test this hypothesis, Olgac and Kurtcuoglu [7▪] extended their revised model to include transport of several CO_2 species and take into account the pH dependence of oxygen–hemoglobin binding. Their results showed that CO_2 is shunted only in small quantities, namely in the range of 1% of the total amount of CO_2 species entering the kidney through the renal artery. In conjunction with the high buffering capacity of blood, only a marginal decrease in arterial pH was seen, which was in addition lower than the decrease in venous pH. Consequently, the Bohr effect appears to impair rather than promote arteriovenous oxygen shunting.

DISCUSSION AND OUTLOOK

Observations that the ratio of blood oxygen concentration between the renal artery and vein stays largely constant over a wide range of blood flow rates provided the initial impetus for investigations of arteriovenous shunting. As experimental approaches could not quantify the actual amount of oxygen shunted, the most recent contributions to the field have relied on computational methods instead.

The most current model [7▪], which stands at the end of an evolutionary development that started with the work of Gardiner *et al.* [8▪], suggests that there is no substantial arteriovenous oxygen shunting in the preglomerular vasculature. In the absence of indications that important physiological or anatomical factors with substantial impact were neglected in that model, it is reasonable to assume that preglomerular shunting is not responsible for the observed constant oxygen concentration between renal artery and vein. As the experimental methods of Levy and Sauceda [1] did not allow for drawing conclusions on the quantity of oxygen shunted,

their results could be explained either by the very small amount of oxygen shunted in the preglomerular vasculature or by shunting in a different part of the kidney.

To serve as the explanation for the behavior of the kidney as a flow-limited organ as was originally proposed, that is an organ in which the supply of oxygen is primarily limited by the flow rate of the incoming blood, oxygen would have to be shunted in large quantities before entering the postglomerular capillary network, as at that level the oxygen is already distributed by the microvasculature throughout the renal parenchyma. However, the underlying observation of a constant ratio of oxygen concentration between renal artery and vein can also be explained by increased glomerular filtration at higher renal blood flows, resulting in greater tubular workload and thus increased oxygen consumption [3].

For oxygen shunting to serve as an effective protection mechanism against both whole kidney hyperoxia and hypoxia, it would also have to take place with substantial magnitude in the preglomerular vasculature. Furthermore, oxygen shunting would need to be increased under hyperoxic conditions and reduced under hypoxic conditions. However, there is no clear evidence for such behavior. The calculations of Olgac and Kurtcuoglu indicated negligible shunting at high arterial inlet blood pO_2 [5▪], and the model of Gardiner *et al.* [8▪] showed a reduction in shunting when renal blood flow and hematocrit were increased. Only when arterial pO_2 was augmented did that model indicate an increase in shunting.

Although shunting would have to occur at the level of the preglomerular vasculature to fulfill its hypothesized role as a protective mechanism or for rendering the kidney a flow-limited organ, it is conceivable that substantial shunting may only occur along postglomerular blood vessels, for example at the level of the peritubular capillaries or along the vasa recta in the medulla. Indeed, Zhang and Edwards [16] demonstrated with a computational model shunting between a subset of the ascending and descending vasa recta.

Quantification of shunting along the postglomerular vasculature is very complex. Although from an anatomic point of view highly simplified models can serve as a stepping stone, it is rather likely that more complex three-dimensional models will be needed to accurately determine oxygen transfer at that location. There is currently insufficient structural data available to produce such models: the small size and large number of postglomerular vessels require micrometer resolution imaging at the organ scale, along with automated processing of the acquired datasets in the terabyte size range. However, with the expected progress in imaging and image processing, it is only a matter of time before we will see the next generation of computational models shedding light on oxygen balance in the entire kidney.

CONCLUSION

In the absence of suitable experimental methods, arteriovenous oxygen shunting has been quantified using computational modeling. The latest of these

Table 1. Overview of computational models examining preglomerular and postglomerular oxygen shunting, and articles discussing the physiologic and pathophysiologic relevance of shunting

	Preglomerular shunting	Postglomerular shunting
Evidence		
Support	1D model, Gardiner *et al.* [8▪] 2D model, Gardiner *et al.* [13] 2D model, Ngo *et al.* [14]	Partial vasa recta model Zhang and Edwards [16]
Do not support	2D model, Ngo *et al.* extrapolated to 3D [6▪] 3D model, Olgac and Kurtcuoglu [7▪]	
Physiologic implications	Renal oxygenation [3] Renal hypoxia response [17]	Corticomedullary oxygen gradient [18] Renal hypoxia response [17]
Pathophysiologic significance	Acute kidney injury [19] Chronic kidney disease [19] and progression to kidney failure [20] Renal anemia [17]	Acute kidney injury [19] Chronic kidney disease [19] Renal anemia [17]

1D, one-dimensional; 2D, two-dimensional; 3D, three-dimensional.

models indicate that although shunting does occur along the preglomerular vasculature, the amount of shunted oxygen is small. They thus neither support the hypothesized role of shunting as a protective mechanism against organ-wide hyperoxia and hypoxia, nor that of rendering the kidney a flow-limited organ. In contrast, the extent of postglomerular shunting and its influence on localized hyperoxia and hypoxia still need to be established (Table 1).

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Levy MN, Sauceda G. Diffusion of oxygen from arterial to venous segments of renal capillaries. Am J Physiol 1959; 196:1336–1339.
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3. Evans RG, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. Am J Physiol Renal Physiol 2008; 295:F1259–F1270.
4. ■ Evans RG, Smith DW, Khan Z, *et al.* Letter to the editor: 'The plausibility of arterial-to-venous oxygen shunting in the kidney: it all depends on radial geometry'. Am J Physiol Renal Physiol 2015; 309:F179–F180.

In this letter, it was argued that wrapping of veins around arteries must be taken into account explicitly in the modeling of preglomerular oxygen transport.

5. ■ Olgac U, Kurtcuoglu V. Renal oxygenation: preglomerular vasculature is an unlikely contributor to renal oxygen shunting. Am J Physiol Renal Physiol 2015; 308:F671–F688.

This publication presents a detailed computational model of preglomerular oxygen transport, questioning the results of previous models by finding no substantial oxygen shunting along the preglomerular vasculature. This model is the basis of the discussions in the two letters of the review period and is also the basis of the revised model published in 2016.

6. ■ Olgac U, Kurtcuoglu V. Reply to 'Letter to the editor: 'The plausibility of arterial-to-venous oxygen shunting in the kidney: it all depends on radial geometry''. Am J Physiol Renal Physiol 2015; 309:F181–F182.

In this letter, it was shown that although explicitly accounting for wrapped vessel pairs yields higher calculated shunting values, the total amount of shunted oxygen remains insubstantial.

7. ■ Olgac U, Kurtcuoglu V. The Bohr effect is not a likely promotor of renal preglomerular oxygen shunting. Front Physiol 2016; 7:482.

In this article, it was shown computationally that explicitly accounting for the effect of various CO_2 species on the hemoglobin–oxygen dissociation curve does not increase but decrease preglomerular oxygen shunting.

8. ■ Gardiner BS, Smith DW, O'Connor PM, Evans RG. A mathematical model of diffusional shunting of oxygen from arteries to veins in the kidney. Am J Physiol Renal Physiol 2011; 300:F1339–F1352.

This publication presents the first one-dimensional hierarchical model of renal preglomerular oxygen shunting. Oxygen shunting was found to be of similar order of magnitude as oxygen consumption in the kidney. The publication contains the hierarchical segment-wise model, explaining the historical context and conceptual basis for the model of Olgac and Kurtcuoglu.

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