Predicting oxygen tension along the ureter

Chang-Joon Lee[1,2], Bruce S. Gardiner[1,2], Roger G. Evans[3] and David W. Smith[2]

[1] School of Science, Health, Engineering and Education, Murdoch University, Perth, Australia.

[2] Faculty of Engineering and Mathematical Sciences, The University of Western Australia, Perth, Australia.

[3]Cardiovascular Disease Program, Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, Australia.

Running title: Oxygen transport in the ureter

Author for correspondence:
David W. Smith
Faculty of Engineering, Computing and Mathematics, The University of Western Australia, M002, 35 Stirling Highway, Crawley, WA 6009, Australia.

Abstract

Continuous measurement of bladder urine oxygen tension (PO_2) is a new method to potentially detect renal medullary hypoxia in patients at risk of acute kidney injury (AKI). To assess its practicality, we developed a computational model of the peristaltic movement of a urine bolus along the ureter and the oxygen exchange between the bolus and ureter wall. This model quantifies the changes in urine PO_2 as it transits from the renal pelvis to the bladder. The model parameters were calibrated using experimental data in rabbits, such that most of the model predictions are within ± 1 standard error (SEM) of the reported mean, with the average percentage difference being 7.0%. Based on parametric studies performed using a model scaled to the geometric dimensions of a human ureter, we found that bladder-urine PO_2 is strongly dependent on the bolus volume (i.e. bolus volume-to-surface area ratio), especially at a volume less than its physiological (baseline) volume (<0.2 ml). For the model assumptions, changes in peristaltic frequency resulted in only a small change in bladder-urine PO_2 (< 1 mmHg). The model also predicted there exists a family of linear relationships of the bladder-urine PO_2 and the pelvic-urine PO_2 for different input conditions. We conclude that it may technically be possible to predict renal medullary PO_2 based on the measurement of bladder-urine PO_2, provided there are accurate real-time measurements of model input parameters. But there are also several modeling uncertainties that must be addressed before the model can be usefully implemented clinically.

Abstract word-count: 248

Key Words: acute kidney injury, ureter, computational model, renal hypoxia, oxygen diffusion

Introduction

Acute kidney injury (AKI) is a common complication experienced by patients in a hospital setting, occurring in conjunction with ~20% of adult admissions and ~30% of pediatric admissions (64). There is growing experimental, clinical and *in silico* evidence that AKI is driven partly by hypoxic injury to renal medullary tissue (22, 43, 59). Thus, continuous monitoring of renal medullary tissue oxygen tension (PO_2) of patients could be beneficial. However, it is not currently feasible to measure PO_2 of renal tissue continuously in human patients.

To this end, continuous measurement of urine PO_2 in patients may provide a useful indirect method of assessing renal medullary PO_2 (23, 24, 39). It is known that there is a correlation between urine PO_2 measured *in vivo* at the renal pelvis (47) with urine in the bladder in human patients. Furthermore, relative good agreement between renal medullary PO_2 and bladder urine PO_2 was observed in anesthetized rabbits (58) and in conscious sheep (52). However, there remains a critical barrier to the use of bladder-urine PO_2 as an indirect measure of renal tissue PO_2. Specifically, the relationship between bladder-urine PO_2 and renal medullary PO_2 is not understood under a variety of conditions. This may confound the interpretations of bladder PO_2 measurements.

Based on our previous investigations, it appears that oxygen diffusion between the urine and the wall of the ureter is the major potential confounder of the relationship between renal medullary tissue PO_2 and bladder urine PO_2 (58). To help resolve this issue, here we develop a two-dimensional (2D) axisymmetric computational model for the ureter that can simulate oxygen exchange between the ureteral tissue and the urine bolus, as the bolus transits along the ureter from the renal pelvis to the bladder. Specifically, this model allows us to quantitatively assess: (1) how closely the bladder-urine PO_2 correlates with the initial urine

PO_2 in the renal pelvis (i.e. pelvic-urine PO_2); and (2) how the rate of urine flow (bolus volume × bolus frequency) influences the measured bladder-urine PO_2; and (3) how the PO_2 of arterial blood (P_aO_2) feeding the ureteral wall tissue influences the measured bladder-urine PO_2.

We begin by describing the details of: (1) model development and calibration of parameter values against experimental data for the rabbit ureter (58); and (2) a series of parametric studies using a model scaled to the geometric dimensions of a human ureter to investigate how the bladder-urine PO_2 changes with changes in pelvic-urine PO_2, urine flow or P_aO_2. We expect the new understanding gained about the relationships between these input parameters and the bladder-urine PO_2 will eventually contribute to the development of an algorithm to enable substantially improved prediction of renal medullary tissue PO_2 from measurements of bladder-urine PO_2 in patients.

Methods

Modeling Overview

Urine is normally transported through the ureter as discrete boluses by peristalsis (8, 41, 65). Each bolus is propelled forward as a moving wave of coordinated smooth muscle (SM) relaxation ahead of the bolus and contraction behind the bolus (20, 30). Our computational model is constructed so that the model's frame of reference moves with the urine bolus, with the bolus having an assumed fixed shape and a constant speed. Oxygen (and other solutes) in the surrounding ureter wall is treated as moving past the stationary bolus. This approach eliminates the need to model a moving peristaltic wave in the ureter wall, which is computationally more expensive. Further, the 3D bolus and ureter wall are modelled utilizing 2D axi-symmetry (with axes r and z), which again affords even greater economy in computational effort. This entire axisymmetric model of urine and ureter wall tissue is hereafter referred to as the 'bolus model'.

The bolus model consists of two components (corresponding to fluid and oxygen transport) of multiple modules, which are semi-coupled (i.e. via a one-way interaction, with fluid flow modules providing advective velocity for the oxygen transport modules) (Fig. 1). Here a module refers to flow and transport equations. The first component comprises three porous media modules (i.e. the 'Darcy flow' modules) describing the fluid transport. One module represents the axial movement of the ureter wall past a stationary bolus. The other two modules represent radial blood flows (i.e. flows normal to the axis of the ureter), in and out of the vasculature of the ureter wall. The second component of the model consists of four oxygen transport modules, which together represent the oxygen transport between the blood vessels and the surrounding tissue in the ureter wall, and oxygen transport between the ureteral tissue and the fluid bolus. These components are solved sequentially, with the fluid flow component being solved first, and then the solutions to the fluid flow equations being

used in the solution of the oxygen transport component. Together, these components predict how bladder-urine PO_2 varies with, for example, pelvic-urine PO_2 (i.e. initial urine PO_2 in the renal pelvis), the rate of urine flow and arterial blood PO_2 (P_aO_2). The bolus model was implemented using COMSOL Multiphysics (Version 5.3, COMSOL, Burlington, MA). The model is publicly available for download at Github (http://github.com/chang-joon/Ureter).

Model Geometry

The idealized 2D axisymmetric geometry of ureter tissue surrounding the urine bolus is shown in Fig. 2. The urine bolus domain is in the shape of a 'comet', with a hemi-spherical head, cylindrical body and tapering 'tail' at the rear of the bolus, based on video-microscopic imaging of distinct urine boluses in rats and humans (8, 65).

The ureter wall domain in the model consists of two sub-domains that represent the three anatomical layers of the ureteral tissue (31, 34): (1) the inner domain representing the merged transitional epithelium and lamina propria, which we refer to as TEL (Transitional Epithelium and Lamina propria); and (2) the outer domain representing the ureter's smooth muscle layer (SM). The transitional epithelium and lamina propria layers were merged into a single domain for computational convenience, since the epithelium layer is typically small (10 - 20% of total thickness, depending on the species) compared to other layers (61, 72).

The ureter wall domains in the model are further divided longitudinally into three regions along the ureteral axis: (1) the pre-bolus region, where the ureter lumen is closed prior to contacting the urine bolus; (2) the urine bolus region, where the ureteral tissue is in contact with the bolus of fluid, with the wall thickness reduced by the radial expansion to accommodate the bolus; and (3) the post-bolus region, where the ureteral lumen is again closed, as the ureter resumes its pre-bolus shape. We assume that the ureteral tissue is incompressible under normal conditions, given the bolus passes within a few seconds and so

there is little time to expel much interstitial or intracellular fluid from the ureteral wall tissue. The change in the thickness of each layer at the bolus region is therefore calculated from the following constant volume relationship:

$$\pi\left(r_{out,0}^2 - r_{in,0}^2\right) = \pi\left(r_{out,1}^2 - r_{in,1}^2\right) \quad [1]$$

where $r_{out,0}$ and $r_{in,0}$ (m) are the outer and inner radii of a layer at the pre-bolus region, respectively, and $r_{out,1}$ and $r_{in,1}$ (m) are the outer and inner radii of a layer at the bolus region, respectively. Note all radii are measured from the longitudinal axis (i.e. z-axis) of the ureter.

Rabbit ureter geometry: The dimensions of the model's ureter and bolus geometry corresponds to rabbits weighing ~3.4 kg (58) (Table 1). The bolus length was set to 14.0 mm and the baseline bolus diameter to 1 mm (29). The bolus volume is then ~0.008 ml. The ureter length was set to 11.5 cm (58, 61). The total ureter wall thickness was set to 0.32 mm, based on the reported histological ureter wall thickness (excluding the adventitia layer) for adult New Zealand white rabbits weighing 2.3 – 3.5 kg (19, 61, 72), corrected for tissue shrinkage during fixation (46). The ureter weight was set to 0.04 g/ureter. We observe this closely matches the measurements reported in Ref (61). The three-layer composition of a rabbit ureter wall consists of 40% TE, 20% LP, and 40% SM (61, 72). Therefore, the thickness of each layer in the rabbit ureter model was set to 0.19 mm for TEL (0.13 mm for TE and 0.06 mm for LP) and 0.13 mm for SM.

Human ureter geometry: The dimensions of the human ureter and bolus geometry are based on reported measurements for the human ureter (6, 26, 32, 62, 72) (Table 1). The bolus length was set to 60 mm and the bolus diameter to 2.5 mm, with a bolus volume of around 0.2 ml (6, 26, 32, 62). The ureter length was set to 30 cm (6, 26). The ureteral wall thickness was set to 2.0 mm based on the reported ureter wall thickness for human (13, 72). A human ureteric wall consisted of ~10% TE, ~30% LP, and ~60% SM (62, 72). Therefore, the thickness of the

109 TEL was set at 0.8 mm (0.2 mm for TE and 0.6 mm for LP) and the thickness of the SM was
110 set at 1.2 mm.

111 For detailed justification of geometric dimensions for rabbit and human bolus models, we
112 refer the readers to the Supplementary Data.

113 **Governing Equations**

114 Here, we briefly outline the governing equations for each fluid flow and oxygen transport
115 modules. For detailed description of how they were derived, we refer the reader to the
116 Supplementary Data.

117 ***Tissue Darcy flow module:*** The governing equation for axial pseudo-flow representing the
118 transition of the urine bolus across the ureter based on Darcy flow through a porous medium
119 is expressed as:

$$\frac{\partial}{\partial \mathrm{t}}(\rho) + \nabla \cdot (\rho \mathbf{v_{bolus}}) = 0 \qquad [2]$$

120 where ρ (kg/m^3) is the (intrinsic) density of blood (assumed to have constant density), t (s) is
121 time, and $\mathbf{v_{bolus}}$ (m/s) is the true velocity of the urine bolus. With the shift in the frame of
122 reference from the tissue to the bolus, we are assuming the tissue is moving past a stationary
123 bolus at the same speed (i.e. $\mathbf{v_{bolus}}$) that the bolus is actually moving along the ureter.

124 ***Arterial and venous Darcy flow modules:*** The governing equations for radial blood flow
125 modules representing the arterial and venous blood flows as Darcy flow through a porous
126 ureteral tissue are expressed as:

$$\frac{\partial}{\partial \mathrm{t}}\left(\rho \epsilon_{\mathrm{p}}\right) + \nabla \cdot (\rho \mathbf{v_d}) = \pm \mathrm{S_{TEL}} \pm \mathrm{S_{SM}} \qquad [3]$$

where ϵ_p is the porosity of the vasculature in the ureteral tissue, $\mathbf{v_d}$ (m/s) is the Darcy velocity of the blood flow ($\mathbf{v_d} = \epsilon_p \mathbf{v_t}$, where $\mathbf{v_t}$ is the true velocity of the blood in a porous medium), $\pm S_{TEL}$ is a flow sink/source in the TEL domain, and $\pm S_{SM}$ is a flow sink/source in the SM domain. The terms S_{TEL} and S_{SM} are negative (oxygen sink or loss) in the arterial flow module, and positive (oxygen source) in the venous flow module.

The flow sink/source in each domain is expressed as:

$$S_i = \frac{f_{Q,i} \cdot Q_{UBF} \cdot \rho}{Vol_i} \quad [4]$$

where $f_{Q,i}$ (unitless) is the fraction of ureteral blood that flows in the domain i, Q_{UBF} (m^3/s) is the total volumetric rate of the ureteral blood flow, and Vol_i (m^3) is the volume of the domain i.

Arterial and venous oxygen transport modules: The governing equation for arterial and venous oxygen transport modules based on the advection-diffusion equation is expressed as:

$$\epsilon_p \left(F_H + c_f^X \frac{\partial F_H}{\partial c_f}\right) \frac{\partial c_f^X}{\partial t} = \nabla \cdot \left(D_{eff} \nabla c_f^X\right) - \mathbf{v_d^X} \cdot \left(F_H + c_f^X \frac{\partial F_H}{\partial c_f}\right) \nabla c_f^X - c_f^X F_H \left(\nabla \cdot \mathbf{v_d^X}\right) \pm c_f^A F_H \left(\nabla \cdot \mathbf{v_d^A}\right) - R_i^X \quad [5]$$

Equation [5] is the general form of oxygen transport equation applied in the arterial and venous oxygen transport modules. The term D_{eff} (m^2/s) is the 'effective' diffusion coefficient ($D_{eff} = \epsilon_p D$; where D (m^2/s) is the oxygen diffusion coefficient in ureteral tissue), $\mathbf{v_d}$ (m/s) is the Darcy velocity calculated from arterial/venous flow modules (equation [3]), and c_f (mol/m^3) is the concentration of free (unbound) oxygen in the blood. The term F_H is derived

from the conventional Hill equation, and is equal to $\left(1 + 4\mathrm{H}\frac{\mathrm{c_f}^{(n-1)}}{(\mathrm{K_H}\sigma)^n + \mathrm{c_f}^n}\right)$, where H (mol/m^3) is the concentration of hemoglobin in whole blood, *n* is a Hill coefficient, $\mathrm{K_H}$ (mmHg) is a Hill function parameter for hemoglobin, and σ (mol/m^3/mmHg) is the solubility coefficient of oxygen in blood. The superscript X refers to either capillaries with arterial blood flow (i.e. blood flowing into the tissue) (X→A) or capillaries with venous blood flow (i.e. blood flowing out of the tissue) (X→V). The terms $-\mathrm{c_f^X F_H}\left(\nabla \cdot \mathbf{v_d^X}\right)$ and $\pm\mathrm{c_f^A F_H}\left(\nabla \cdot \mathbf{v_d^A}\right)$ cancel each other out exactly for the arterial oxygen transport module (i.e. $\pm\mathrm{c_f^A F_H}\left(\nabla \cdot \mathbf{v_d^A}\right)$ is a positive term in the arterial module), but not for the venous oxygen transport module (i.e. $\pm\mathrm{c_f^A F_H}\left(\nabla \cdot \mathbf{v_d^A}\right)$ is a negative term).

The term $-\mathrm{R}_i^{\mathrm{X}}$ in equation [4] is an oxygen sink representing the loss of oxygen from the blood to the tissue, which can be written as:

$$\mathrm{R}_i^{\mathrm{A}} = \alpha_i\left(\mathrm{c_f^{cap}} - \mathrm{c_f^T}\right) \cdot f_{\mathrm{A}} \qquad [6]$$

$$\mathrm{R}_i^{\mathrm{V}} = \alpha_i\left(\mathrm{c_f^{cap}} - \mathrm{c_f^T}\right) \cdot (1 - f_{\mathrm{A}}) \qquad [7]$$

where α_i (1/s) is a constant representing the oxygen mass transfer coefficient between the capillaries and the ureteral tissue in the domain *i*, $\mathrm{c_f^{cap}}$ (mol/m^3) is the weighted-average free oxygen concentration in the ureteral capillaries (set to ($0.1 \times \mathrm{c_f^A} + 0.9 \times \mathrm{c_f^V}$), where superscripts A and V refer to arterial blood and venous blood, respectively), $\mathrm{c_f^T}$ (mol/m^3) is the free oxygen concentration in the ureteral tissue, and f_{A} (unitless) is the fraction of oxygen lost to the tissue by the arterial blood. Note that equations [5], [6] and [7] were applied only to the bolus region, on the assumption that the oxygen supply and consumption are at equilibrium at pre- and post-bolus regions.

Tissue oxygen transport module: The governing equation for oxygen transport in the ureteral tissue is expressed in the form of a standard advection-diffusion equation:

$$\frac{\partial c_f^T}{\partial t} = \nabla \cdot \left(D \nabla c_f^T\right) - \mathbf{v_{bolus}} \cdot \nabla c_f^T + R_i^T - R_i^{VO2} \quad [8]$$

where superscript T denotes ureteral wall tissue. The term R_i^T is an oxygen source term representing the oxygen supplied by the blood to the tissue, and is a sum of oxygen sinks R_i^A and R_i^V in equations [6] and [7]. The term R_i^{VO2} (mol/m^3/s) is the oxygen sink term representing the oxygen consumed by the ureteral tissue in domain *i*, expressed as:

$$R_i^{VO2} = -\dot{V}O_{2,i} \cdot \left(\frac{c_f^T}{K_M + c_f^T}\right) \quad [9]$$

The term $\dot{V}O_{2,i}$ (mol/m^3/s) is the rate of oxygen consumption per volume in the domain *i*. The term $\frac{c_f^T}{K_M + c_f^T}$ represents the aerobic/anaerobic metabolism transition in the ureteral tissue. The constant K_M represents the oxygen concentration (expressed in terms of mol/m^3) at which half the cellular energy production is derived from aerobic metabolism and half is derived from anaerobic metabolism.

Bolus oxygen transport module: The governing equation for oxygen transport within the bolus is expressed as:

$$\frac{\partial c_f^B}{\partial t} = \nabla \cdot \left(D^B \nabla c_f^B\right) \quad [10]$$

where superscript B denotes the urine bolus. The term D^B (m^2/s) is the oxygen diffusion coefficient for the bolus, which is set to be much larger (×100) than the free diffusion coefficient for oxygen because the oxygen in the small volume of bolus is well mixed due to fluid circulation within a traveling bolus.

Boundary conditions

Darcy flow modules: For the arterial and venous Darcy flow modules, a pressure boundary condition ($p = 0$) is applied at the outer boundary of the SM domain and a no-flow boundary condition ($\mathbf{v_d} = 0$) is applied at remaining boundaries. For the tissue Darcy flow module, a pressure boundary condition ($p = 0$) is applied at the top boundary of the pre-bolus domains and an outlet boundary condition ($\mathbf{v_d} = \mathbf{v_{bolus}}$) is applied at the bottom boundary of the post-bolus. A no flow boundary condition is applied at all remaining boundaries.

Oxygen transport modules: For the arterial oxygen transport module, a constant concentration boundary condition ($c_f^A = \sigma P_a O_2$) is applied at the outer boundary of the SM domain, and a zero diffusive flux boundary condition ($D\nabla c_f^A = 0$) is applied at the remaining boundaries. For the venous oxygen transport module, a zero diffusive flux boundary condition ($D\nabla c_f^V = 0$) is applied to all boundaries.

A Robin boundary condition is applied at the bolus-ureter boundary where the bolus and the internal wall of the ureter meet. The Robin boundary condition is defined as:

$$\mathbf{n} \cdot \mathbf{J^X} = \pm h\left(c_f^T - c_f^B\right) \qquad [11]$$

where $\mathbf{n}$ is a unit vector, $\mathbf{J}$ is the oxygen flux across the bolus-ureter boundary, and the superscript X could signify either flux out of the tissue (T) or into the bolus (B). This boundary condition determines how much oxygen is transported from the ureteral tissue to the bolus, or vice versa. For the tissue module the right-hand side is negative, and for the bolus module it is positive. The term h (m/s) is a constant called the oxygen conductivity coefficient, which represents the 'resistance to oxygen transport' in the transitional epithelium layer. The magnitude of this term is unknown, for as far as the authors are aware this has not been reported in the literature. Therefore, we fitted the model solutions using a

range of possible values against experimental data reported in (58), and chose the h value that yielded the best fit (see Results).

For the tissue oxygen transport module, a constant concentration boundary condition ($c_f^T = \sigma PO_2^T$, where PO_2^T is the tissue oxygen tension as the urine bolus enters the ureter) was applied at the top boundary of the pre-bolus domains, and a zero diffusive flux boundary condition ($D\nabla c_f^T = 0$) was applied at the bottom boundary of the post-bolus domains. A zero-flux boundary condition ($\mathbf{J^T} = 0$) was set at the remaining external boundaries. Because the model is axisymmetric, an axial symmetry boundary condition was applied at the center axis (i.e. at r = 0).

Baseline Parameter Selection for the Rabbit Ureter Model

In this section, we briefly outline the baseline parameter values selected for the rabbit ureter model. For detailed justification of the selected values, we refer the reader to the Supplementary Data.

The baseline ureteral blood flow (UBF) was set to 100 ml/min/100 g tissue, a compromise value between datasets from anesthetized Sprague-Dawley rats (50), anesthetized female rabbits (2, 3), and the reported blood flow in other 'peristaltic tissues' in anesthetized dogs (7) and rats (63). This translates to UBF of 0.04 ml/min for a single ureter with a volume of 37 mm^3 and weight of 0.04 g.

The baseline rate of oxygen consumption in the ureter ($\dot{V}O_2$) was set to 0.04 $mol \cdot m^{-3} \cdot s^{-1}$, or about 1.3×10^{-9} mol/s for baseline UBF of 0.04 ml/min. For comparison the reported $\dot{V}O_2$ ranges from 0.0023 – 0.0025 $mol \cdot m^{-3} \cdot s^{-1}$ (38, 70) in the rabbit bladder, 0.016 $mol \cdot m^{-3} \cdot s^{-1}$in the canine small intestine (7), and between 0.03 – 0.04 $mol \cdot m^{-3} \cdot s^{-1}$ in the rat small intestine (63). So this estimate is substantially higher than the bladder $\dot{V}O_2$, but is consistent with the VO_2 in similar peristaltic tissues, such as the rat small intestine.

Oxygen transport in the ureter

We have distributed the $\dot{V}O_2$ per volume as 40% in the SM and 60% in the TEL, based on the reported $\dot{V}O_2$ per volume in the bladder mucosa (i.e. TEL layer) (1, 38). Thus, the $\dot{V}O_{2,SM}$ of the rabbit ureter is 0.03 $mol \cdot m^{-3} \cdot s^{-1}$ (or 7.15×10^{-10} mol/s for a single whole ureter), and the $\dot{V}O_{2,TEL}$ is 0.045 $mol \cdot m^{-3} \cdot s^{-1}$ (or 5.84×10^{-10} mol/s). The critical PO_2 at which the metabolism in the ureteral tissue transition from aerobic to anaerobic was set to 1 mmHg (14), and so the value of the constant K_M to 0.00134 mol/m^3 (i.e. $\sigma \times 1$ mmHg).

The chosen baseline UBF and $\dot{V}O_2$ were used as an initial starting point for the model calibration.

The porosity (ϵ_p) in the arterial and venous modules (equations [3] and [5]) is defined as the ratio of the total cross-sectional area of the vessels to the total cross-sectional area of the tissue at a particular level of the ureter. Using the relationship between the ϵ_p, $\mathbf{v_{UBF}}$ (true velocity of the ureteral blood flow) and $\mathbf{v_d}$ $\left(\epsilon_p = \frac{\mathbf{v_d}}{\mathbf{v_{UBF}}}\right)$, for baseline UBF of 0.04 ml/min and capillary blood velocity of ~1 mm/s (5, 25, 37, 49, 74), the baseline ϵ_p at the external boundary of the SM domain is found to be around 0.002. At the inner wall, we assumed there is only a small fraction (5%) of the total UBF, which results in $\mathbf{v_d}$ of about 1.33×10^{-4} mm/s. So the ϵ_p at the inner wall is 1.33×10^{-4}.

The baseline blood parameter values were set to match those reported in Ref (58) for calibration purposes. Therefore, the baseline hemoglobin concentration (H) was set to 1.81 mol/m^3 (hematocrit of ~35%) and the baseline P_aO_2 was set to 110 mmHg (58). The baseline Hill function parameter (K_H) was set to 27 mmHg (15, 40, 57), and the Hill function coefficient (n) was set to 2.7 (40). The blood density (ρ) was assumed constant throughout the ureter at 1050 kg/m^3 (36). The solubility coefficient of oxygen in blood (σ) was set to 1.34 $\mu mol \cdot l^{-1} \cdot mmHg^{-1}$ (40).

The baseline physiological diffusion coefficient (D) for oxygen in the ureteral tissue was set to 2.8×10^{-9} m^2/s in accordance with Refs (27, 28).

The baseline urine bolus velocity ($\mathbf{v_{bolus}}$) in rabbits was interpolated from urine velocities reported in other species, namely, rats (65), dogs (6, 66, 71), pigs (54, 67, 73) and humans (6, 9, 17, 48, 73), normalized by the body weight. From these data, we interpolated the normalized urine velocity for rabbits weighing 3.5 kg to be about 4.33 $mm \cdot s^{-1} \cdot kg^{-1}$, with an absolute $\mathbf{v_{bolus}}$ of about 15.2 mm/s. Hence, we have set the baseline $\mathbf{v_{bolus}}$ to 15.2 mm/s, and baseline transit time ($t_{transit}$; the time taken for the urine to travel from the renal pelvis to the bladder) to 7.6 s for the rabbit bolus model.

Modification of Baseline Parameter Values Specific to the Human Ureter Model

Most of the parameter values for the human ureter model are identical to those in the rabbit ureter model. Here, we outline parameter values that have been modified specifically for the human ureter model.

The baseline UBF per unit volume of tissue in the human model was the same as that used for the rabbit model, i.e. 100 ml/min/100 g tissue as was set in the rabbit model. This is equivalent to 3.8 ml/min/ureter for a single ureter estimated to weigh about 3.8 g (based on the length of 30 cm and the thickness of 2 mm).

We have set the baseline H to match the normal H in humans, which is typically about 2.33 mol/m^3 (normal hematocrit level of ~45% (4, 33)). The baseline (*in vivo*) P_aO_2 was set to 90 mmHg (12).

The baseline $\mathbf{v_{bolus}}$ for human ureter model was set to 20 mm/s (17). Consequently, the baseline $t_{transit}$ for humans was set to 15 s (for the ureter length of 30 cm).

All model parameters for rabbit and human models are summarized in Table 2.

Model Calibration

The model parameters were calibrated against experimental data reported by Sgouralis et al (58). In that experiment, Sgouralis et al infused isotonic saline solutions with three different mean PO_2 (2.1 mmHg, 111.0 mmHg, and 159 mmHg) into an anesthetized rabbit ureter at various rates of flow (1.0, 0.5, 0.25 and 0.1 ml/min) and measured the corresponding PO_2 of the solution in the bladder. The model was calibrated against the reported bladder-urine PO_2 for each initial solution PO_2 and rate of flow. The primary model input parameters were UBF, $\dot{V}O_2$, fluid (bolus) velocity, $t_{transit}$, h, and α_i. Four of these parameters were designated as fitting parameters: UBF, $\dot{V}O_2$, h, and α_i. Parameter values for non-fitting parameters (fluid velocity and $t_{transit}$) are listed in Table 3. The values are in accordance with those reported in Ref (58).

Assuming a bolus volume of 0.008 ml, the infusion rates employed in the experiment reported by Sgouralis et al implies a very high peristaltic frequency of between 13 to 125 boluses/min, compared to a normal peristaltic frequency of ~4 boluses/min in the rabbit ureter (58). In such a limiting case of high bolus frequency, the fluid flow in the experiment can be simplified to a continuous flow through an open tube. So we created what we refer to as the 'continuous flow model', or CF model to serve as a baseline model for modeling the experiment by Sgouralis et al (58). The details of how the CF model was created can be found in the Supplementary Data. It is expected that the solution for the limiting case of a head-to-tail 'bolus train' model will be nearly identical to the solution of the CF model, and so using this assumption, the experimental data reported in Sgouralis et al (58) can be used as a pathway to validating the bolus model.

The calibration of the model parameters was done in two stages (Fig. 3). In the first stage, the simulations used the CF model with baseline UBF and $\dot{V}O_2$. Parameters h and α_i where then gradually adjusted from an initial guess until the best-fit solution to the experimental data was

found. In the second stage, simulations were carried out using the bolus model with the same values of UBF and $\dot{V}O_2$ found in the first stage of calibration. The solutions from the bolus model were compared against those from the CF model and the experimental data from Ref (58). In both stages of the calibration, the parameter value for $t_{transit}$ was set to its experimentally measured value (and so was not adjusted). The fluid (bolus) velocity for each rate of isotonic saline flow was estimated from the reported transit time and the ureter length. The model solution was deemed acceptable if the predicted value lay within ± 2 standard errors (SEMs) of the measured means.

To simulate continuous flow, the bolus diameter in the bolus model was adjusted to match the urine flow diameter in the CF model. Due to the potentially many simulations required for calibration, the bolus length in the bolus model was shortened from its original length of 14 mm to 6 mm, to save computational cost. Note that in this case the bolus length does not affect the final solution since we are simulating a continuous flow by a continuous train of boluses end to end.

Several (3 – 5) iterations were required to obtain the final equilibrium solution, with convergence monitored by the solution from the previous iteration acting as the initial and boundary conditions for the next iteration. Specifically, the ureteral tissue PO_2 at the ‘tail’ of the bolus in the preceding iteration becomes the concentration boundary condition at the bolus ‘head’ in the subsequent iteration. This is repeated until convergence of head and tail PO_2. The final average ureteral tissue PO_2 over the ureter domains in the preceding iteration also become the initial condition in the subsequent iteration. Each iteration represented individual boluses traveling as a continuous train.

Numerical Methods

The governing equations were solved numerically by the finite-element method (FEM) using COMSOL Multiphysics 5.3. Up to 170,000 triangular mesh elements were employed for the bolus model, and up to 210,000 elements for the CF model, with quadratic interpolation functions. All simulations were carried out using a Dell PC with an Intel Core i7 3.40-GHz CPU running Windows 7 Professional. Each simulation typically took less than two minutes.

Parametric Study Using the Human Bolus Model

The bladder-urine PO_2 depends on several factors, such as pelvic-urine PO_2 (which determines the initial PO_2 employed in the ureter model), P_aO_2 and ureteral tissue $\dot{V}O_2$ (which chiefly determine the ureteral tissue PO_2), and the rate of urine flow (which determines the time available for diffusive mass transfer between the tissue and the bolus of urine, and the urine bolus volume). Here, we limited the scope of the study to consider only the effects of variations in pelvic-urine PO_2, P_aO_2 and the rate of urine flow on bladder-urine PO_2.

Comparison of baseline cases between rabbit and human ureter models: In both rabbit and human ureter models, identical input parameter values were set and the resulting bladder-urine PO_2 were compared. Specifically, the pelvic-urine PO_2 was set to 10 mmHg, P_aO_2 was set to 90 mmHg, and the hematocrit was set to 45%.

Effects of variation in pelvic-urine PO_2: Focusing on the hypoxic kidney, we simulated pelvic-urine PO_2 ranging from 0 to 30 mmHg. The pelvic-urine PO_2 at the low end of this range is clearly indicative of severe renal hypoxia. The upper bound chosen was based on the urine PO_2 of ~30 mmHg at the renal papilla under normal physiological condition, as estimated from our renal medullary oxygen transport model (44). This value is also close to that measured experimentally *in vivo* in conscious sheep (10) and anesthetized humans (47).

Effects of variation in P_aO_2: Three levels of P_aO_2 were tested: 90, 150, and 300 mmHg. The value of 90 mmHg is the *in vivo* P_aO_2 under normoxic condition (21, 68), and the value of 300 mmHg is the expected P_aO_2 in a surgical or intensive care setting with an inspired oxygen content of 60% (39, 69). The value of 150 mmHg is an intermediate P_aO_2.

Effects of variation in urine flow: The urine flow per ureter is a function of the product of bolus volume and peristaltic frequency. We varied the urine flow in the bolus model by changing either the bolus volume (0.03, 0.1, 0.2, 0.4, and 0.8 ml/bolus) independently of frequency, or changing the peristaltic frequency (0.5, 1.5, 3, 6, and 12/min) independently of volume. Either method results in urine flows of 0.1, 0.3, 0.6, 1.2 and 2.4 ml/min/ureter (baseline bolus volume = 0.2 ml, frequency = 3/min and flow rate of 0.6 ml/min/ureter). For the cases of increased peristaltic frequency, we assumed that under normal conditions the bolus frequency does not affect the initial PO_2, or the $\dot{V}O_2$ in the ureteral tissue.

Results

Calibration of the CF Model and the Bolus Model Against Experimental Data

In the first stage of calibration for the CF model, we initially tested the model using the baseline UBF of 0.04 ml/min and $\dot{V}O_2$ of 0.04 mol·m^{-3}·s^{-1} (see Parameter Selection), with an initial guess for h = 1.0 × 10^{-4} m/s (the oxygen conductivity coefficient that determines the magnitude of oxygen flux across the ureter wall; see equation [11]) and calibrated the values of UBF, $\dot{V}O_2$ and h until the resulting bladder-urine PO_2 were close to the observed experimental mean values reported in Ref (58) (i.e. to within ±2 SEM).

Perhaps unsurprisingly, the initial predictions did not fit very well to the experimental data, especially for the low urine flow of 0.1 ml/min (Table 4). The best-fit predictions to the experimental data resulted when the $\dot{V}O_2$ was increased twofold (0.07 mol·m^{-3}·s^{-1}) and h was set to 5.0 × 10^{-4} m/s, while the UBF remained unchanged (see Table 4 and Fig. 4). Most of the predictions were then within, or close to, ± 1 SEM of that observed experimentally in Ref (58). The largest PO_2 difference between predicted and reported values was found for the high urine flow (1 ml/min) and high proximal ureter PO_2 (160 mmHg) case, where the difference was approximately 14 mmHg (~9%). When the oxygen exchange between the tissue and the urine is set to zero (i.e. as occurs at steady state in a no urine flow condition), the predicted ureteral tissue PO_2 should be close to the measured tissue PO_2 for the conditions of the experiment. Indeed, the calibrated model ureteral tissue PO_2 is close to the no flow tissue PO_2 reported in Ref (58) (33.0 mmHg predicted vs 34.5 mmHg reported).

In the second stage of calibration for the bolus model, the same combination of UBF and $\dot{V}O_2$ that produced the best-fit for the CF model (i.e. UBF of 0.04 ml/min and $\dot{V}O_2$ of 0.07 mol·m^{-3}·s^{-1}) were used as initial values.

The best-fit solutions for the bolus model to the experimental data of Ref (58) was found when the initial $\dot{V}O_2$ was reduced by 20% to 0.064 mol·m^{-3}·s^{-1} while the UBF remained the same at 0.04 ml/min, and the h value was adjusted down 95% to 3.0 × 10^{-5} m/s. For these conditions the predicted ureteral tissue PO_2 at zero urine flow was found to be 33 mmHg (similar to the CF model). In general, the best-fit solutions of the bolus model closely matched the experimental data reported in Ref (58) (Table 5 and Fig. 4), demonstrating that the bolus model can accurately predict the urinary PO_2 even for a limiting case such as continuous flow of urine. The bolus model was usually more accurate than the CF model, particularly at low flow rates (Fig. 4). The average percentage difference between the model predictions and the experimental data for all rates of flow was 13.7% for the CF model versus 7.0% for the bolus model. At low flow rates (i.e. 0.1 and 0.25 ml/min), the difference was 16.2% for the CF model versus 3.9% for the bolus model (Table 5).

Comparison of Urine Bolus PO_2 in the Rabbit and in the Human

With identical baseline UBF (100 ml/min/100 g tissue), $\dot{V}O_2$ (0.064 mol/m^3/s), and P_aO_2 (90 mmHg), the rabbit model predicted ureteral tissue PO_2 of around 31 mmHg, while the human model predicted ureteral tissue PO_2 of around 30 mmHg. Therefore, the initial conditions in the ureter wall of both species were close to each other.

For the base case, the rabbit ureter model predicted the bladder-urine PO_2 after the transit time of 7.6 s of 22.4 mmHg (a 12.4 mmHg increase from initial PO_2 of 10 mmHg), while the human ureter model predicted the bladder-urine PO_2 after the transit time of 15 s of 18.9 mmHg (a 8.9 mmHg increase from initial PO_2).

Effects of Pelvic-Urine PO_2, Arterial Blood PO_2 and Urine Flow on the Bladder-Urine PO_2

We remind the readers that the parametric studies presented in this section were performed using human ureter model.

Rate of change in urine bolus PO_2: The model predicts that the rate of change of urine PO_2 with respect to time increases as the pelvic-urine PO_2 decreases (Fig. 5A; P_aO_2 = 90 mmHg; urine volume = 0.2 ml/bolus). In addition, the rate of change in urine PO_2 increases as the P_aO_2 increases from 90 mmHg to 300 mmHg (Fig. 5B), because the increase in P_aO_2 effectively increases the ureteral tissue PO_2 (from ~30 mmHg to ~42 mmHg) and so this increases the PO_2 gradient between the ureteral tissue and the urine bolus.

The change in urine flow per ureter is a function of the product of bolus volume and peristaltic frequency. When the urine flow increased solely due to the increase in bolus volume, the rate of change in urine PO_2 decreased (Fig. 5C). However, when the urine flow increased solely due to the increase in peristaltic frequency, there was virtually no difference in the rate of change in urine PO_2 (Fig. 5D). The likely explanation for this is that we have assumed in the model that there is no increase in oxygen consumption associated with increased peristaltic frequency. The model then predicts only a small decrease in the ureteral tissue PO_2 as peristaltic frequency increases (from 30 mmHg at normal frequency to 28 mmHg at four times the normal frequency). Further, the transit time (i.e. the time during which ureteral-bolus diffusion can occur) and the arterial blood supply (i.e. P_aO_2) to the bolus region in the model are assumed to be constant, and so are independent of the frequency. Consequently, the model predicted similar rate of change in urine PO_2 and absolute urine PO_2 for different peristaltic frequencies.

The predicted effects of increasing bolus volume or peristaltic frequency are further illustrated in Fig. 6. A large change in the bladder-urine PO_2 is seen (in Fig. 6) to occur when the urine flow is a function of bolus volume, but bladder-urine PO_2 remains almost constant when the change in urine flow is a function of altered peristaltic frequency. What is important to note is the change in bladder-urine PO_2 per bolus volume is greater when the bolus volume is less than 0.2 ml (i.e. baseline physiological volume) regardless of P_aO_2 or initial pelvic-

urine PO_2, which suggests urine PO_2 becomes increasingly more sensitive once the bolus volume falls below a certain threshold.

Relationship between initial pelvic-urine PO_2 and final bladder-urine PO_2: The predicted bladder-urine PO_2 varies linearly with the pelvic-urine PO_2, regardless of P_aO_2 or urine flow (i.e. bolus volume) (Fig. 7). This suggests that it may be possible to predict the pelvic-urine PO_2 for a given measured bladder-urine PO_2 using a family of simple linear relationships for different values of arterial PO_2 and urine flow. Note the effect of peristaltic frequency on the relationship between pelvic- and bladder-urine PO_2 is negligible (Fig. 6). Therefore, we remind readers that the change in urine flow in this section (Figs. 7 and 8) refers to the change in urine flow as a function of bolus volume.

The model predicts that, for the same pelvic-urine PO_2, the bladder-urine PO_2 decreases as the urine flow increases (i.e. bolus volume increased) (Fig. 7). Decreased urine flow also results in a steeper linear relationship between the pelvic-urine PO_2 and the bladder-urine PO_2 (Fig. 7) (gradient of 1.77 for urine flow of 0.6 ml/min/ureter compared to 1.34 for 2.4 ml/min/ureter; arterial PO_2 = 90 mmHg; Table 6).

An increase in P_aO_2 from 90 mmHg to 300 mmHg increased the ureteral tissue PO_2 from ~30 mmHg to ~42 mmHg. This 12 mmHg increase in ureteral tissue PO_2 raised the bladder-urine PO_2 by ~3 mmHg, from 13.3 mmHg to 16.3 mmHg (Figs. 7A and 7C). The gradient of the linear relationship between pelvic-urine PO_2 and bladder-urine PO_2 remained relatively constant (<4% difference; Table 6) with variations in P_aO_2 from 90 to 300 mmHg and only varied significantly between different rates of urine flow.

The model predicts a steep change in bladder-urine PO_2 when urine flow is less than ~0.5 ml/min/ureter (Fig. 8). This steep change in bladder-urine PO_2 is present regardless of pelvic-urine PO_2; decreasing sharply when the pelvic-urine PO_2 is higher than the tissue PO_2 (30

mmHg under normoxic conditions and 42 mmHg under hyperoxic condition) and increasing when the pelvic-urine PO_2 is less than the tissue PO_2. Based on extrapolation of bladder-urine PO_2 at higher rates of urine flow, it is predicted that at near zero urine flow, the bladder-urine PO_2 will reach its final PO_2 of around 27 mmHg under normoxic condition, and around 31 mmHg under hyperoxic condition (at transit time of 15 s). From extrapolation of the changes in tissue PO_2, it is also predicted that the ureteral tissue PO_2 at near zero urine flow will be around 27 mmHg under normoxic condition, and 36 mmHg under hyperoxic conditions (data not shown). So under near zero urine flow and normoxic conditions, the bolus PO_2 is likely to have reached equilibrium with that in the ureteral wall before it reaches the bladder. However, under hyperoxic conditions, the bolus reaches the bladder before it reaches an equilibrium with the ureteral wall.

Discussion

We have developed a novel 2D axisymmetric computational model of a ureter in both rabbits and humans, comprising the urine bolus and the surrounding ureteral tissue. A continuous flow (CF), non-bolus model was also developed for comparison, including with previous studies. The model parameters were calibrated against experimental observations of fluid PO_2 in the ureter of the rabbit (58). Using the calibrated parameter values, both the CF model and the bolus model yielded a good fit to the experimental data reported in Ref (58), with most of the predictions being within ± 1 SEM of the mean values reported for the experiment.

Following the calibration of the model, we performed a series of parametric studies to investigate the influence of pelvic-urine PO_2, P_aO_2, and urine flow (as a function of either bolus volume or peristaltic frequency) on human bladder-urine PO_2. It has been proposed previously that bladder-urine PO_2 could be measured during major surgery or other in-patient clinical situations to indirectly assess renal oxygenation (24). The predictions from the modified human ureter model indicate that: (1) Under identical baseline conditions, the transfer of information about renal medullary tissue PO_2 to the urine may be comparatively more confounded in rabbits than in humans, mainly due to the relatively larger bolus volume-to-surface area ratio for humans; (2) Bladder-urine PO_2 is strongly dependent on the urine bolus volume, resulting in a very high bladder-urine PO_2 when the bolus volume is less than its physiological (baseline) volume; (3) Changes in urine flow due to changes in peristaltic frequency, under the assumptions of the model, make very little difference to the rate of change in urine PO_2 as it passes down the ureter and thus little difference to bladder-urine PO_2; and (4) There exists a family of linear relationships between the bladder-urine PO_2 and the pelvic-urine PO_2 for different combinations of P_aO_2 and urine flow. These findings, taken collectively, suggest that it may technically be possible to predict pelvic-urine PO_2 and subsequently renal medullary PO_2 based on the measurement of bladder-urine PO_2, provided

urine flow and arterial PO_2 can also be continuously monitored. However, there are several limitations and uncertainties in the model that must be addressed before the model can be implemented clinically (*vide infra*).

Comparison of the Bolus Model and the CF Model

While both the bolus model and the CF model predictions were within the accepted margin of error (i.e. ± 2 SEM), the bolus model predictions were generally a better-fit to the experimental data in Ref (58) than the CF model predictions. This is likely due to the CF model being simpler in its construction and a less accurate physiologically representation. For example, because the CF model treats the urine as a single continuous stream, it does not distinguish between different regions of the ureter relative to the urine (i.e. pre-bolus, bolus, and post-bolus regions). The CF model also does not have a separate oxygen transport module for the ureteral tissue whereas the bolus model does. Together, these simplifications likely result in less accurate estimation of the local oxygen concentration gradient between the ureter and the urine, and consequently less accurate estimation of urine PO_2 compared with the bolus model.

Sgouralis et al (58) also developed a model of oxygen transport along the ureter that predicts the bladder-urine PO_2 using a set of two equations describing conservation of oxygen in three compartments: ureteral tissue, bloodstream (combining both arterial and venous blood flow as one), and urine. We note that the predictions of the model by Sgouralis et al (58) (we will refer to this model as the "Sgouralis model") were also mostly within the accepted margin of error but were less accurate compared to our bolus model. For example, the difference between the measured PO_2 and the predicted PO_2 at flow rate of 1.0 ml/min and proximal ureter PO_2 of 160 mmHg was ~30 mmHg for the Sgouralis model compared to ~10 mmHg for our bolus model. We suspect the difference in accuracy between the two models may be because the Sgouralis model treated the tissue PO_2 as spatially uniform and fixed over time (a

510 'lumped model'), so unlike our bolus model, it does not take into account the radial variance
511 of ureteral tissue PO_2. This may lead to inaccurate estimate of the PO_2 gradient between the
512 tissue and the urine at the urine-ureter interface resulting in less accurate predictions of the
513 urine PO_2.

514 ***Effectiveness of urine PO_2 as a biomarker for monitoring AKI***

515 According to our model, urine PO_2 is strongly dependent on the condition of a patient at a
516 particular time, especially on the urine bolus volume. Assuming constant peristaltic
517 frequency, the bladder-urine PO_2 rapidly approached the ureter tissue PO_2 as the bolus
518 volume decreased. This finding accords with those from a study of the dog ureter by Rennie
519 et al (53) and the study of the rabbit ureter by Sgouralis et al (58), both of which found that as
520 the rate of urine flow progressively decreased, the bladder-urine PO_2 approached the
521 presumed ureteral tissue PO_2 in their respective experimental animals. The higher bladder-
522 urine PO_2 at lower urine bolus volume as predicted in our model is likely due to the smaller
523 urine bolus volume-to-surface area ratio (0.57 mm^3/mm^2 for the baseline urine bolus volume
524 of 0.2 ml versus 0.22 mm^3/mm^2 for bolus volume of 0.03 ml, assuming the shape and the
525 length of the bolus does not change with bolus volume). As the volume-to-surface area ratio
526 increases, the amount of free oxygen required to increase the PO_2 in the bolus volume also
527 increases, while the amount of oxygen diffused per unit time (determined by diffusive flux ×
528 surface area) decreases due to less relative surface area. A similar result was predicted when
529 comparing rabbit and human ureters under similar condition (i.e. identical UBF, $\dot{V}O_2$ per
530 volume of tissue, and oxygen conductivity coefficient h). The difference in the urine bolus
531 volume-to-surface area ratio between the two species (0.23 mm^3/mm^2 for the rabbit versus
532 0.56 mm^3/mm^2 for the human) resulted in higher bladder-urine PO_2 in rabbit than in human
533 despite the shorter transit time in rabbit (7.6 s vs 15.0 s).

In our simulations, a marked increase in bladder-urine PO_2 occurs when the bolus volume falls below the physiological (baseline) value of 0.2 ml, meaning that the risk of a significant loss of information regarding renal medullary PO_2 increases when the patient cannot produce urine with a bolus volume that is larger than normal (i.e. > 0.2 ml). Therefore, diuretic conditions should be ideally maintained so that the predictive value of bladder-urine PO_2 can be preserved. Our observations are also relevant to considering the potential utility of continuous measurement of urinary PO_2 under the varying clinical conditions when patients are at risk of AKI. For example, continuous measurement of urinary PO_2 may be more useful during cardiac surgery requiring cardiopulmonary bypass, during which patients often experience a brisk diuresis (52), or during administration of radiocontrast agents when preceded by volume loading (51), than during oliguric AKI. However, we note that our conclusion is limited to the assumptions of the model, namely the assumption of constant bolus length. We have assumed that the urine bolus retains its typical comet shape and the bolus length does not change with the bolus volume, but the bolus length in humans can range from 30 to 120 mm (6). It is also reported that the bolus volume of urine can increase by a factor of 100 in polyuria compared with the volume in oliguria (56). Although the change in the shape of the bolus was not reported in Ref (56), it is reasonable to expect that the bolus geometry will change to some extent as the volume changes by a factor of 100. Relaxing this assumption will affect the overall volume-to-surface area ratio and likely change the predictions of the model to an unknown extent. One possible scenario is where the bolus volume-to-surface area ratio is maintained as the bolus volume decreases, likely resulting in less increase in urinary PO_2 than predicted by the current model.

Unlike the bolus volume, peristaltic frequency had little impact on bladder-urine PO_2 in the model (< 1 mmHg). This result is a consequence of the assumption in the model that $\dot{V}O_2$ in the ureteral tissue does not change with peristaltic frequency, which effectively keeps the

559 tissue PO_2 in the model constant. This assumption was made mainly because the total ureteral
560 $\dot{V}O_2$ appears to be dominated by the basal component (i.e. the 'basal $\dot{V}O_2$' occurring in the
561 mucosa, is 60% greater than the basal $\dot{V}O_2$ in the SM) of the total $\dot{V}O_2$ (38). In practice,
562 ureteral $\dot{V}O_2$ is likely to increase with peristaltic frequency due to the extra mechanical work
563 performed by ureteral SM. Changes in the frequency or rate of propagation of peristaltic
564 waves by the SM could potentially be triggered by changes in urine flow (16), or by
565 hormonal (11), or neural stimuli (18), among other factors. The extent to which ureteral $\dot{V}O_2$
566 increases with peristaltic frequency is unknown, but any increase in $\dot{V}O_2$ with peristaltic
567 frequency will likely result in lower bladder-urine PO_2 than the value predicted by the current
568 model. This is one of the critical uncertainties in the model that should be addressed in future
569 studies.

570 The predicted effects of changes in urine flow on bladder-urine PO_2 differed according to
571 whether the changes were associated with altered bolus volume or peristaltic frequency. For
572 as we have demonstrated in our simulations, the difference in the predicted urine PO_2
573 between the increase in bolus volume and the increase in peristaltic frequency (for the same
574 urine flow) can be as high as 5 mmHg. This observation suggests that knowledge of both the
575 bolus volume and frequency of peristalsis may be required to make an accurate prediction of
576 pelvic urine PO_2 from a measure of bladder-urine PO_2. In a clinical situation, this information
577 would be very difficult to generate by non-invasive methods. According to Saeki et al (55),
578 bolus volume and peristaltic frequency change independently from each other, resulting in
579 different patterns of change in the two parameters. However, available evidence indicates that
580 the frequency and rate of propagation of peristaltic waves do not vary in a systematic manner
581 with urine flow (60, 66). Thus, it may be reasonable to simply assume that changes in urine
582 flow are exclusively associated with changes in the bolus volume. This assumption could
583 potentially be tested experimentally.

For our modeling assumptions, we observed a family of linear relationships between the bladder-urine PO_2 and the pelvic-urine PO_2 for different combinations of P_aO_2 and urine flow. These linear relationships, at least in theory, allow the prediction of the pelvic-urine PO_2 and subsequently the renal medullary PO_2 based on the measurement of bladder-urine PO_2. Even at very low urine flow, where the loss of information on renal medullary PO_2 is likely to be highest, it may be possible to adjust for any distortions (i.e. increase) in the bladder-urine PO_2 by using the linear relationship between bladder- and pelvic-urine PO_2, similar to the one that is shown in Fig. 7. However, this is only possible when the changes in all the input parameters, including urine flow (ideally as a product of both bolus volume and peristaltic frequency) and P_aO_2, are carefully monitored in real-time.

Model Limitations and Uncertainties

Some of the major parameter values for the ureter model, namely UBF, $\dot{V}O_2$ and oxygen conductivity coefficient h, were only calibrated against one experimental dataset. We also assumed that UBF and $\dot{V}O_2$ (and effectively the ureter tissue PO_2) remained constant, but this assumption may not be true in practice. As physiological conditions change in patients at risk of AKI, the UBF and $\dot{V}O_2$ may also change and alter the ureter tissue PO_2 to an unknown extent. These issues may possibly be addressed through future experimentation.

We have also assumed the shape of the bolus, the geometry of the ureter, and the speed of the bolus movement, and consequently, transit time from the renal pelvis to the bladder along ureters that vary in length (from left to right kidney and from person to person) are all known, and that these parameters remain constant along the ureter's length. In other words, we assumed that the 'average patient' will have the same combination of bolus shape, ureteral geometry and transit time, although each patient in practice will have a different combination of parameters resulting in different predicted urine PO_2. These uncertainties may have a

major effect on the model prediction and so its clinical value. For example, if the transit time doubled from the baseline value of 15 s to 30 s (say as a result of decreased bolus velocity or increase in ureter length or some combination of the two), then the predicted bladder-urine PO_2 increases from 13.3 mmHg to 20.5 mmHg, assuming an initial PO_2 = 0 mmHg and a normal urine flow of 0.6 ml/min/ureter. At a lower urine flow of say 0.1 ml/min/ureter, the predicted bladder-urine PO_2 increases from 22.5 mmHg to 26.9 mmHg. The predicted ureteral tissue PO_2 is about 27 mmHg at low urine flow, so the urine bolus traveling at half the baseline velocity, or through a longer ureter, has practically reached equilibrium with the ureteral wall by the time it reaches the bladder. This example demonstrates how the uncertainty in transit time can have a major effect on the model prediction and its clinical interpretation. Similar examples could be given for bolus shape, renal pelvic PO_2, ureter wall blood flow and ureter wall PO_2.

The model assumes the initial pelvic-urine PO_2 does not differ from the renal papilla PO_2 and is known prior to the simulation. However, experimental data from Leonhardt et al (47) suggest that the normal pelvic-urine PO_2 may be up to 15 mmHg higher than the renal papilla PO_2. Presumably, the magnitude of this difference depends on urine residence time in the renal pelvis. At a lower frequency, more time is available for interaction between the renal pelvic wall and the urine, resulting in a higher initial pelvic-urine PO_2. In other words, the initial pelvic-urine PO_2 in the model becomes dependent on peristaltic frequency, and this dependency must be known before an accurate prediction can be made. Therefore, to resolve this structural uncertainty, it appears that another module of urine in the renal pelvis is required before the current ureter model. The said module would capture the residence-time dependency of pelvic-urine PO_2 as peristaltic frequency changes and provide a better estimate of initial pelvic-urine PO_2.

The oxygen conductivity coefficient h is a critical parameter in the model that represents the overall resistance to oxygen transport at the ureter-urine interface. One of the resistances is the ‘dead zone’ of fluid in the bolus (i.e. the fluid boundary layer that remains near stagnant as fluid swirls around inside the bolus). The thickness of the near stationary boundary layer in the fluid will depend on the roughness of the surface of the transitional epithelium, which could be affected by factors such as the sloughing of cells or mucosal secretions. Another resistance to oxygen transport is the cell layers in the TE and its basement membrane, which contain no capillaries. It has been suggested that keratin may be involved in this membrane structure (35), and so may provide some additional resistance depending on the amount of keratin (or other proteins) accumulated in the transitional epithelium, as well as the overall thickness of cell layers making up the transitional epithelium. The oxygen conductivity coefficient will therefore be determined by the sum of the thicknesses of the above-mentioned layers. This total thickness may vary between subjects to an unknown extent, thereby contributing additional uncertainty to the model.

The bolus model does not include the longitudinal blood flow with respect to the ureter wall. When the reference of frame is shifted from the ureter to the moving urine bolus, there is a component of blood flow, or specifically oxygenated hemoglobin flux, that moves along the ureter wall, with ‘new blood’ flowing longitudinally into the urine bolus head, and ‘old blood’ flowing longitudinally out of the urine bolus tail. For simplicity, this longitudinal oxygenated hemoglobin flux was not included in the bolus model

Further, the bolus model can also be extended to include the different ways the blood may flow within the tissue of the ureter wall, as the wall pressure rises as a urine bolus passes. One example of internal pressure and muscle contraction profoundly influencing tissue blood supply, is when the blood flow to heart tissue temporarily stops as the heart contracts in systole. If this happens in the ureter, then the blood ‘flow’ in our model would be purely

longitudinal along the bolus. That is, the blood flows past the bolus as does the tissue, but it does not flow in or out of the tissue (i.e. no radial blood flow) as the bolus passes. Another important issue is whether the bolus, if sufficiently large, squeezes the blood out of the tissue, partially or completely, and there is limited or no oxygen source to replenish the oxygen consumed by or lost to the bolus within the tissue. Such analysis can be done by 'switching off' the blood flow modules in the model.

Future directions

In this study, we showed that an adequate urine bolus volume (and ensuing ratio of bolus volume-to-surface area) is critical to reducing the increase in urine PO_2 along the course of the ureter, and thus minimizing the loss of information on the renal medullary PO_2 status obtained from bladder-urine PO_2 measurements. However, we also point out that the conclusions drawn from this study are limited to the assumptions made in the model which are subject to numerous uncertainties as above. These uncertainties and variabilities of model input parameters such as bolus geometry, transit time, ureter wall blood flow and ureter wall $\dot{V}O_2$ must be carefully addressed in future studies before we can move forward to clinical application, such as employing the model for management of renal medullary tissue PO_2 from measurements of bladder-urine PO_2 in patients.

Once the uncertainties in the ureter model have been addressed, the focus can shift to integrating our previously developed cardiac-renal perfusion model (42), and renal oxygenation models (44-46), with the ureter model from this study, into a 'virtual kidney' model of renal oxygen transport. A virtual kidney will allow us to simulate various clinical scenarios (e.g. changes in perfusion, hematocrit, urine flow or bladder-urine PO_2) and kidney states, to better understand their implications on renal medullary tissue PO_2. These

simulations can be then used to suggest potential interventions to improve renal medullary tissue PO_2, and thus facilitate efforts to minimize in the incidence of AKI.

Word count: 9395

Grants

We wish to acknowledge funding from the National Health and Medical Research Council of Australia (NHMRC) project grant funding GNT606601 and GNT1122455, and Medical Health and Research Grant funding (Rounds 20 and 21) from the Western Australian Department of Health.

Additional Information

Readers are herein alerted that Supplementary section containing detailed justification of model geometry and model parameters, and formulation of governing equations, and model file are publicly available for download at Github (http://github.chang-joon/Ureter).

Reference

1. **Andersson K-E, Boedtkjer DB, and Forman A**. The link between vascular dysfunction, bladder ischemia, and aging bladder dysfunction. *Ther Adv Urol* 9: 11-27, 2017.
2. **Batra S, Bjellin L, Iosif S, Martensson L, and Sjogren C**. Effect of oestrogen and progesterone on the blood flow in the lower urinary tract of the rabbit. *Acta Physiol Scand* 123: 191-194, 1985.
3. **Batra S, Bjellin L, Sjogren C, Iosif S, and Widmark E**. Increases in blood flow of the female rabbit urethra following low dose estrogens. *J Urol* 136: 1360-1362, 1986.
4. **Billett H**. Hemoglobin and hematocrit. In: *Clinical Methods: the History, Physical, and Laboratory Examinations* edited by Walker H, Hall W, and Hurst J. Boston: Butterworth Publishers, 1990.
5. **Bottcher W, and Steinhausen M**. Microcirculation of the renal papilla of rats under control conditions and after temporary ischemia. *Kidney Int Suppl* 6: S74-80, 1976.
6. **Boyarsky S, and Labay PC**. Ureteral dimensions and specifications for bioengineering modeling. In: *Urodynamics*, edited by Boyarsky S, Tanagho EA, Gottschalk CW, and Zimskind PD. New York: Academic Press, 1971, p. 163-165.
7. **Bulkley GB, Kvietys PR, Parks DA, Perry MA, and Granger DN**. Relationship of blood flow and oxygen consumption to ischemic injury in the canine small intestine. *Gastroenterology* 89: 852-857, 1985.
8. **Burge HJ, Middleton WD, McClennan BL, and Hildebolt CF**. Ureteral jets in healthy subjects and in patients with unilateral ureteral calculi: comparison with color Doppler US. *Radiology* 180: 437-442, 1991.
9. **Butcher HR, Jr., and Sleator W, Jr.** A study of the electrical activity of intact and partially mobilized human ureters. *J Urol* 73: 970-986, 1955.
10. **Calzavacca P, Evans RG, Bailey M, Lankadeva YR, Bellomo R, and May CN**. Long-term measurement of renal cortical and medullary tissue oxygenation and perfusion in unanesthetized sheep. *Am J Physiol Regul Integr Comp Physiol* 308: R832-839, 2015.
11. **Catacutan-Labay P, and Boyarsky S**. Bradykinin: effect on ureteral peristalsis. *Science* 151: 78-79, 1966.
12. **Cattermole GN, Leung PYM, Ho GYL, Lau PWS, Chan CPY, Chan SSW, Smith BE, Graham CA, and Rainer TH**. The normal ranges of cardiovascular parameters measured using the ultrasonic cardiac output monitor. *Physiol Rep* 5: e13195, 2017.
13. **Cheng J, Wang Y, Wu J, and Hong N**. Upper urinary tract abnormalities in patients with late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: Computed tomography imaging characteristics. *Radiol Infect Dis* 2: 88-93, 2015.
14. **Cohen JJ**. Is the function of the renal papilla coupled exclusively to an anaerobic pattern of metabolism? *Am J Physiol Renal Physiol* 236: F423-F433, 1979.
15. **Collier CR**. Oxygen affinity of human blood in presence of carbon monoxide. *J Appl Physiol* 40: 487-490, 1976.
16. **Constantinou CE, and Yamaguchi O**. Multiple-coupled pacemaker system in renal pelvis of the unicalyceal kidney. *Am J Physiol Regul Integr Comp Physiol* 241: R412-R418, 1981.
17. **Davenport K, Timoney AG, and Keeley FX, Jr.** Effect of smooth muscle relaxant drugs on proximal human ureteric activity in vivo: a pilot study. *Urol Res* 35: 207-213, 2007.
18. **Del Tacca M, Lecchini S, Stacchini B, Tonini M, Frigo GM, Mazzanti L, and Crema A**. Pharmacological studies of the rabbit and human renal pelvis. *Naunyn Schmiedebergs Arch Pharmacol* 285: 209-222, 1974.
19. **Douglas GC, and Hossler FE**. Vascular anatomy of the rabbit ureter. *Anat Rec* 242: 47-56, 1995.

20. **Dwyer TM, and Schmidt-Nielsen B**. The renal pelvis: machinery that concentrates urine in the papilla. *News Physiol Sci* 18: 1-6, 2003.
21. **Evans RG, Goddard D, Eppel GA, and O'Connor PM**. Stability of tissue PO2 in the face of altered perfusion: a phenomenon specific to the renal cortex and independent of resting renal oxygen consumption. *Clin Exp Pharmacol Physiol* 38: 247-254, 2011.
22. **Evans RG, Ince C, Joles JA, Smith DW, May CN, O'Connor PM, and Gardiner BS**. Haemodynamic influences on kidney oxygenation: clinical implications of integrative physiology. *Clin Exp Pharmacol Physiol* 40: 106-122, 2013.
23. **Evans RG, Lankadeva YR, Cochrane AD, Marino B, Iguchi N, Zhu MZL, Hood SG, Smith JA, Bellomo R, Gardiner BS, Lee C-J, Smith DW, and May CN**. Renal haemodynamics and oxygenation during and after cardiac surgery and cardiopulmonary bypass. *Acta Physiol (Oxf)* 222: e12995, 2018.
24. **Evans RG, Smith JA, Wright C, Gardiner BS, Smith DW, and Cochrane AD**. Urinary oxygen tension: a clinical window on the health of the renal medulla? *Am J Physiol Regul Integr Comp Physiol* 306: R45-50, 2014.
25. **Farrugia E, Lockhart JC, and Larson TS**. Relation between vasa recta blood flow and renal interstitial hydrostatic pressure during pressure natriuresis. *Circ Res* 71: 1153-1158, 1992.
26. **Frober R**. Surgical anatomy of the ureter. *BJU Int* 100: 949-965, 2007.
27. **Gardiner BS, Smith DW, O'Connor PM, and Evans RG**. A mathematical model of diffusional shunting of oxygen from arteries to veins in the kidney. *Am J Physiol Renal Physiol* 300: F1339-F1352, 2011.
28. **Gardiner BS, Thompson SL, Ngo JP, Smith DW, Abdelkader A, Broughton BRS, Bertram JF, and Evans RG**. Diffusive oxygen shunting between vessels in the preglomerular renal vasculature: anatomic observations and computational modeling. *Am J Physiol Renal Physiol* 303: F605-F618, 2012.
29. **Gould DW, Hsieh AC, and Tinckler LF**. The behaviour of the intact ureter in dogs, rabbits and rats. *J Physiol* 129: 436-447, 1955.
30. **Griffiths DJ**. Flow of urine through the ureter: a collapsible, muscular tube undergoing peristalsis. *Journal of biomechanical engineering* 111: 206-211, 1989.
31. **Hanna MK, Jeffs RD, Sturgess JM, and Barkin M**. Ureteral structure and ultrastructure. Part I. The normal human ureter. *J Urol* 116: 718-724, 1976.
32. **Harada T, Noto H, Etori K, Kumasaki T, Kigure T, Nishizawa O, and Tsuchida S**. The estimation of urine bolus volume for patients with congenital hydronephrosis. *Nihon Heikatsukin Gakkai Zasshi* 21: 455-466, 1985.
33. **Hawkins WW, Speck E, and Leonard VG**. Variation of the hemoglobin level with age and sex. *Blood* 9: 999-1007, 1954.
34. **Hicks RM**. The fine structure of the transitional epithelium of rat ureter. *J Cell Biol* 26: 25-48, 1965.
35. **Hicks RM**. The permeability of rat transitional epithelium. Kertinization and the barrier to water. *J Cell Biol* 28: 21-31, 1966.
36. **Hinghofer-Szalkay H, and Greenleaf JE**. Continuous monitoring of blood volume changes in humans. *J Appl Physiol (1985)* 63: 1003-1007, 1987.
37. **Holliger C, Lemley KV, Schmitt SL, Thomas FC, Robertson CR, and Jamison RL**. Direct determination of vasa recta blood flow in the rat renal papilla. *Circ Res* 53: 401-413, 1983.
38. **Hypolite JA, Longhurst PA, Gong C, Briscoe J, Wein AJ, and Levin RM**. Metabolic studies on rabbit bladder smooth muscle and mucosa. *Molecular and cellular biochemistry* 125: 35-42, 1993.

39. **Kainuma M, Yamada M, and Miyake T**. Continuous urine oxygen tension monitoring in patients undergoing cardiac surgery. *Journal of cardiothoracic and vascular anesthesia* 10: 603-608, 1996.
40. **Keener JS, James.** *Mathematical physiology*. New York: Springer New York, 1998.
41. **Kim S, Jacob JS, Kim DC, Rivera R, Lim RP, and Lee VS**. Time-resolved dynamic contrast-enhanced MR urography for the evaluation of ureteral peristalsis: initial experience. *J Magn Reson Imaging* 28: 1293-1298, 2008.
42. **Lee C-J, Gardiner BS, and Smith DW**. A cardiovascular model for renal perfusion during cardiopulmonary bypass surgery. *Comput Biol Med* 119: 103676, 2020.
43. **Lee CJ, Gardiner BS, Evans RG, and Smith DW**. Analysis of the critical determinants of renal medullary oxygenation. *Am J Physiol Renal Physiol* 2019.
44. **Lee CJ, Gardiner BS, Evans RG, and Smith DW**. A model of oxygen transport in the rat renal medulla. *Am J Physiol Renal Physiol* 315: F1787-F1811, 2018.
45. **Lee CJ, Gardiner BS, Ngo JP, Kar S, Evans RG, and Smith DW**. Accounting for oxygen in the renal cortex: a computational study of factors that predispose the cortex to hypoxia. *Am J Physiol Renal Physiol* 313: F218-F236, 2017.
46. **Lee CJ, Ngo JP, Kar S, Gardiner BS, Evans RG, and Smith DW**. A pseudo-three-dimensional model for quantification of oxygen diffusion from preglomerular arteries to renal tissue and renal venous blood. *Am J Physiol Renal Physiol* 313: F237-F253, 2017.
47. **Leonhardt KO, Landes RR, and McCauley RT**. Anatomy and physiology of intrarenal oxygen tension: preliminary study of the effects of anesthetics. *Anesthesiology* 26: 648-658, 1965.
48. **Lewis CA, Coptcoat MJ, Carter SS, Hilson AJ, Wickham JE, and Shah PJ**. Radionuclide imaging of ureteric peristalsis. *Br J Urol* 63: 144-148, 1989.
49. **Lockhart JC, Larson TS, and Knox FG**. Perfusion pressure and volume status determine the microvascular response of the rat kidney to NG-monomethyl-L-arginine. *Circ Res* 75: 829-835, 1994.
50. **Mooney EF, Geraghty JG, O'Connell M, Kent P, Angerson W, Quereshi A, Sarazen A, and Fitzpatrick JM**. Radiotracer measurement of ureteric blood flow. *J Urol* 152: 1022-1024, 1994.
51. **Navaneethan SD, Singh S, Appasamy S, Wing RE, and Sehgal AR**. Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Am J Kidney Dis* 53: 617-627, 2009.
52. **Ngo JP, Lankadeva YR, Zhu MZL, Martin A, Kanki M, Cochrane AD, Smith JA, Thrift AG, May CN, and Evans RG**. Factors that confound the prediction of renal medullary oxygenation and risk of acute kidney injury from measurement of bladder urine oxygen tension. *Acta Physiol (Oxf)* 227: e13294, 2019.
53. **Rennie DW, Reeves RB, and Pappenheimer JR**. Oxygen pressure in urine and its relation to intrarenal blood flow. *Am J Physiol* 195: 120-132, 1958.
54. **Roshani H, Dabhoiwala NF, Dijkhuis T, Kurth KH, and Lamers WH**. An in vivo endoluminal ultrasonographic study of peristaltic activity ni the distal porcine ureter. *J Urol* 163: 602-606, 2000.
55. **Saeki H, Morita T, Nishimoto T, Kondo S, and Tsuchida S**. Changes in the ureteral peristaltic rate and the bolus volume in gradual and rapid urinary flow increase. *Tohoku J Exp Med* 146: 273-275, 1985.
56. **Saeki H, Morita T, Weiss RM, and Miyagawa I**. The role of ureteral peristaltic rate and bolus volume on increasing urine flow. *Urol Int* 41: 174-179, 1986.
57. **Severinghaus JW**. Blood gas calculator. *J Appl Physiol* 21: 1108-1116, 1966.
58. **Sgouralis I, Kett MM, Ow CPC, Abdelkader A, Layton AT, Gardiner BS, Smith DW, Lankadeva YR, and Evans RG**. Bladder urine oxygen tension for assessing renal

medullary oxygenation in rabbits: experimental and modeling studies. *Am J Physiol Regul Integr Comp Physiol* 311: R532-R544, 2016.
59. **Singh P, Ricksten S-E, Bragadottir G, Redfors B, and Nordquist L**. Renal oxygenation and haemodynamics in acute kidney injury and chronic kidney disease. *Clin Exp Pharmacol Physiol* 40: 138-147, 2013.
60. **Sleator W, Jr., and Butcher HR, Jr.** Action potentials and pressure changes in ureteral peristaltic waves. *Am J Physiol* 180: 261-276, 1955.
61. **Sokolis DP**. Identification and characterisation of regional variations in the material properties of ureter according to microstructure. *Comput Methods Biomech Biomed Engin* 17: 1653-1670, 2014.
62. **Sokolis DP, Petsepe DC, Papadodima SA, and Kourkoulis SK**. Age- and region-related changes in the biomechanical properties and composition of the human ureter. *J Biomech* 51: 57-64, 2017.
63. **Stevenson NR, and Weiss HR**. Blood flow, O2 extraction and O2 consumption along the rat small intestine. *Microvasc Res* 35: 278-286, 1988.
64. **Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL, and Acute Kidney Injury Advisory Group of the American Society of N**. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 8: 1482-1493, 2013.
65. **Tillig B, and Constantinou CE**. Videomicroscopic imaging of ureteral peristaltic function in rats during cystometry. *J Pharmacol Toxicol Methods* 35: 191-202, 1996.
66. **Tsuchida S**. Computer analyses of urometrographic and electro-ureterographic data on the ureteral function at various urine flow rates. *Tohoku J Exp Med* 97: 297-310, 1969.
67. **Venkatesh R, Landman J, Minor SD, Lee DI, Rehman J, Vanlangendonck R, Ragab M, Morrissey K, Sundaram CP, and Clayman RV**. Impact of a double-pigtail stent on ureteral peristalsis in the porcine model: initial studies using a novel implantable magnetic sensor. *J Endourol* 19: 170-176, 2005.
68. **Weinberger SE, Cockrill BA, and Mandel J**. *Principles of Pulmonary Medicine E-Book*. Philadelphia: Elsevier Health Sciences, 2017.
69. **Weld KJ, Montiglio C, Lacy G, Bush AC, and Cespedes RD**. The effects of ureteral mobilization and transection on ureteral oxygenation. *Urology* 71: 1035-1038, 2008.
70. **Wendt IR, and Gibbs CL**. Energy expenditure of longitudinal smooth muscle of rabbit urinary bladder. *Am J Physiol* 252: C88-96, 1987.
71. **William Sleator J, and Harvey R. Butcher J**. Action potentials and pressure changes in ureteral peristaltic waves. *Am J Physiol* 180: 261-276, 1955.
72. **Wolf JS, Jr., Humphrey PA, Rayala HJ, Gardner SM, Mackey RB, and Clayman RV**. Comparative ureteral microanatomy. *J Endourol* 10: 527-531, 1996.
73. **Young AJ, Acher PL, Lynn B, McCahy PJ, and Miller RA**. Evaluation of novel technique for studying ureteral function in vivo. *J Endourol* 21: 94-99, 2007.
74. **Zimmerhackl B, Robertson CR, and Jamison RL**. Fluid uptake in the renal papilla by vasa recta estimated by two methods simultaneously. *Am J Physiol Renal Physiol* 248: F347-F353, 1985.

Tables

Table 1. List of major dimensions for the rabbit and human bolus models

Parameter	Species	Baseline Value	Reported Range	Reference(s)
Ureter length (cm)	Rabbit	11.5	11.5	(58, 61)
	Human	30.0	25 – 37	(6, 26)
Ureter thickness (mm)	Rabbit	0.32	0.23 – 0.32	(19, 61, 72)
	Human	2.0	1.35 – 2.5	(13, 72)
Bolus length (mm)	Rabbit	14.0	N/A	(29)
	Human	60.0	30 – 120	(6)
Bolus radius (mm)	Rabbit	0.5	0.3 – 0.5	(29, 58)
	Human	1.25	1 – 4	(6)
Bolus volume (ml)	Rabbit	0.008	0.008	Estimated
	Human	0.2	0.1 – 0.6	(6, 32)
TE thickness (mm)	Rabbit	0.13	(37 – 43% of total thickness)	(61, 72)
	Human	0.2	(5 – 19% of total thickness)	(62, 72)
LP thickness (mm)	Rabbit	0.06	(19 – 21% of total thickness)	(61, 72)
	Human	0.6	(27 – 30% of total thickness)	(62, 72)
SM thickness (mm)	Rabbit	0.13	(38 – 42% of total thickness)	(61, 72)
	Human	1.2	(54 – 65% of total thickness)	(62, 72)

Abbreviations: TE = transitional epithelium. LP = lamina propria. SM = smooth muscle.

Table 2. List of baseline model parameters for rabbit and human bolus models

Parameter	Symbol	Species	Baseline Value
Ureteral blood flow	UBF	Rabbit	0.04 ml/min
		Human	3.8 ml/min
Oxygen consumption in the SM per volume	$\dot{V}O_{2,SM}/Vol_{SM}$	Rabbit	0.03 $mol \cdot m^{-3} \cdot s^{-1}$
		Human	0.054 $mol \cdot m^{-3} \cdot s^{-1}$
Oxygen consumption in the TEL per volume	$\dot{V}O_{2,TEL}/Vol_{TEL}$	Rabbit	0.045 $mol \cdot m^{-3} \cdot s^{-1}$
		Human	0.081 $mol \cdot m^{-3} \cdot s^{-1}$
Total oxygen consumption per volume	$\dot{V}O_{2,T}/Vol_{T}$	Rabbit	0.035 $mol \cdot m^{-3} \cdot s^{-1}$
		Human	0.064 $mol \cdot m^{-3} \cdot s^{-1}$
Anaerobic transition threshold	K_M	Rabbit & Human	0.00134 mol/m^3
Density of blood	ρ	Both	1050 kg/m^3
Hematocrit	Hct	Rabbit	35%*
		Human	45%
Hemoglobin concentration in whole blood	H	Rabbit	1.81 mol/m^3
		Human	2.33 mol/m^3
Solubility	σ	Both	1.34 $\mu mol \cdot l^{-1} \cdot mmHg^{-1}$
Hill function parameter	K	Both	27 mmHg
Hill function coefficient	n	Both	2.7
Arterial oxygen tension	P_aO_2	Rabbit	110 mmHg*
		Human	90 mmHg
Oxygen diffusion coefficient in ureteral tissue	D	Both	2.8×10^{-9} m^2/s
Effective oxygen diffusion coefficient in capillaries in the bolus model	D_{eff}	Both	$(2.8 \times 10^{-9} \cdot \epsilon_p)$ m^2/s

Oxygen transport in the ureter

Oxygen diffusion coefficient in the urine bolus	D^B	Both	2.8×10^{-7} m^2/s
Urine bolus velocity	$\mathbf{v_{bolus}}$	Rabbit	15 mm/s
		Human	20 mm/s
Transit time	$t_{transit}$	Rabbit	7.6 s
		Human	15 s

*Used specifically for model calibration only. Abbreviations: TEL = transitional epithelium & lamina propria. SM = smooth muscle.

Table 3. List of fluid velocities and transit times used for model calibration

	Value			
Parameter	**1 ml/min**	**0.5 ml/min**	**0.25 ml/min**	**0.1 ml/min**
Fluid (bolus) velocity (mm/s)	32.9	19.5	11.6	5.8
Total Transit Time (s)	3.5	5.9	9.9	19.7

Parameter values from Ref (58) for four rates of urine flow (1, 0.5, 0.25, and 0.1 ml/min).

Table 4. Urine PO_2 predictions by the CF model after initial and final first-stage calibration

Urine Flow Rate (ml/min)	Calibration Stage	UBF (ml/min)	$\dot{V}O_{2,T}/Vol_T$ (mol/s/m^3)	h (m/s)	Ureter Tissue PO_2 (mmHg)[a]	Proximal Ureter PO_2 (mmHg)[b]	Bladder-Urine PO_2 (mmHg)[c]
0.1	Initial	0.04	0.04	1×10^{-4}	44.2	2	39.9 (25.5%)
						110	55.9 (53.6%)
						160	62.9 (69.1%)
	Final	0.04	0.07	5×10^{-4}	33.0	2	32.3 (1.6%)
						110	43.1 (18.4%)
						160	47.1 (26.6%)
0.25	Initial	0.04	0.04	1×10^{-4}	44.2	2	29.4 (-1.7%)
						110	70.6 (46.5%)
						160	91.2 (41.0%)
	Final	0.04	0.07	5×10^{-4}	33.0	2	25.3 (-15.4%)
						110	57.9 (20.1%)
						160	74.3 (14.8%)
0.5	Initial	0.04	0.04	1×10^{-4}	44.2	2	21.8 (-4.4%)
						110	80.4 (36.0%)
						160	116.6 (17.3%)

						2	19.7 (-13.6%)
	Final	0.04	0.07	5×10^{-4}	33.0	110	70.0 (18.4%)
						160	97.8 (-1.6%)
						2	15.5 (-18.8%)
	Initial	0.04	0.04	1×10^{-4}	44.2	110	89.1 (11.2%)
						160	130.5 (-1.3%)
1.0						2	14.9 (-22.0%)
	Final	0.04	0.07	5×10^{-4}	33.0	110	80.8 (0.9%)
						160	117.8 (-10.9%)

UBF, ureteral blood flow; $\dot{V}O_{2,T}/Vol_T$, total ureteral oxygen consumption per volume tissue; h, oxygen conductivity coefficient. [a]Predicted by the CF model under conditions of no urine flow. [b]From Ref (58). [c]Model-predicted value. The values in parentheses represent the percentage difference between model prediction and measured PO_2 (i.e. (Predicted PO_2 – Measured PO_2) / Measured PO_2 × 100). See Fig. 4 for a graphical comparison between model predictions and experimental data.

Table 5. Urine PO_2 predictions by the bolus model after initial and final second-stage calibration

Urine Flow Rate (ml/min)	Calibration Stage	UBF (ml/min)	$\dot{V}O_{2,T}/Vol_T$ (mol/s/m^3)	h (m/s)	Ureter Tissue PO_2 (mmHg)[a]	Proximal Ureter PO_2 (mmHg)[b]	Bladder-Urine PO_2 (mmHg)[c]
0.1	Initial	0.04	0.07	5×10^{-4}	30.8	2	33.4 (5.0%)
						110	33.4 (-8.2%)
						160	33.4 (-10.2%)
	Final	0.04	0.06	3×10^{-5}	32.6	2	32.9 (3.5%)
						110	36.1 (-0.8%)
						160	37.9 (1.9%)
0.25	Initial	0.04	0.07	5×10^{-4}	30.8	2	33.3 (12.0%)
						110	33.8 (-29.9%)
						160	34.0 (-47.4%)
	Final	0.04	0.06	3×10^{-5}	32.6	2	27.4 (-8.4%)
						110	50.0 (3.7%)
						160	61.4 (-5.1%)
0.5	Initial	0.04	0.07	5×10^{-4}	30.8	2	32.6 (43.0%)
						110	34.6 (-41.5%)
						160	35.6 (-64.2%)
	Final	0.04	0.06	3×10^{-5}	32.6	2	20.5 (-10.1%)

						110	64.2 (8.6%)
						160	89.6 (-9.9%)
1.0	Initial	0.04	0.07	5×10^{-4}	30.8	2	32.4 (69.6%)
						110	38.8 (-51.6%)
						160	43.6 (-67.0%)
	Final	0.04	0.06	3×10^{-5}	32.6	2	15.3 (-19.9%)
						110	79.2 (-1.1%)
						160	117.6 (-11.0%)

UBF, ureteral blood flow; $\dot{V}O_{2,T}/Vol_T$, total ureteral oxygen consumption per volume tissue; h, oxygen conductivity coefficient. [a]Predicted by the bolus model under conditions of no urine flow. [b]From Ref (58). [c]Model-predicted value. The values in parentheses represent the percentage difference between model prediction and measured PO_2 (i.e. (Predicted PO_2 – Measured PO_2) / Measured PO_2 × 100). See Fig. 4 for a graphical comparison between model predictions and experimental data.

Table 6. Gradient of a linear relationship between pelvic-urine PO_2 and bladder-urine PO_2

P_aO_2 (mmHg)	UF = 0.3		UF = 0.6[a]		UF = 1.2		UF = 2.4	
	k	**Δ*k* (%)**	***k***	**Δ*k* (%)**	***k***	**Δ*k* (%)**	***k***	**Δ*k* (%)**
90	2.30	-	1.77	-	1.57	-	1.34	-
150	2.23	-2.8	1.76	-0.6	1.58	-0.8	1.33	-1.0
300	2.22	-3.3	1.75	-0.8	1.60	-1.9	1.32	-2.1

UF, urine flow (ml/min/ureter); P_aO_2, arterial blood oxygen tension; k, gradient of pelvic-urine PO_2 and bladder-urine PO_2 relationship $\left(\frac{\Delta pelvic\ PO_2}{\Delta bladder\ PO_2}\right)$; and Δ*k*, percentage change from *k* at P_aO_2 = 90 mmHg. [a]Baseline urine flow rate.

Figure Legends

Fig. 1. Schematic representation of the bolus model and its modules. The bolus model consists of the three Darcy flow modules (left) and four oxygen transport modules (right). *Left*: The blood enters the radial arterial flow module (A), transitions to the radial venous flow module and leaves as venous blood (V). Relative to a stationary bolus (bolus not shown in diagram), the ureter tissue undergoes axial flow past the bolus. *Right*: The concentration of oxygen at the inlet of the arterial oxygen transport module (A) is equal to arterial oxygen tension (P_aO_2). The oxygen in the arterial blood transitions to the venous side and leaves the vein with a concentration determined by the venous oxygen tension (P_vO_2 given by oxygen transport module (V)). The arteries and veins also lose oxygen to the tissue module, as part of oxygen consumption in the tissue (the veins may also gain oxygen depending on the tissue PO_2). Oxygen may also diffuse between the ureter tissue and the urine bolus. The Darcy flow modules provide information on the velocities of blood and tissue flow, in the form of Darcy flow, to the oxygen transport modules, which in turn solve for the oxygen concentration in each module, subject to appropriate boundary and initial conditions.

Fig. 2. Idealized geometry of the ureter and the urine bolus. In the bolus model, the ureter wall is divided into two domains. The TEL domain represents the merged lamina propria with overlying transitional epithelium (for computational convenience) and the SM domain represents the smooth muscle layers within the wall of the ureter. The ureter wall domains are further divided longitudinally into three regions along the ureteral axis: (i) the pre-bolus region, (ii) the bolus region, and (iii) the post-bolus region. At the bolus region, the expanded (i.e. thinned, but constant volume) ureter wall domains surround the bolus domain, which represents the space occupied by the urine bolus traveling along the ureter. The bolus domain is in the shape of a ‘comet’, with a hemi-spherical head, a cylindrical body, and a tapering ‘tail’ region.

Fig. 3. Flow chart of model calibration process. The first stage of the calibration process started with the continuous flow (CF) model, using baseline UBF and $\dot{V}O_2$ in Table 2 as initial values. If the model prediction exceeded ± 2 SEM of the mean bladder-urine PO_2 reported by Sgouralis et al (58), then UBF and $\dot{V}O_2$ were adjusted to yield a better fit with the reported data. Once the best-fit solution was found, the second stage of calibration process was conducted for the bolus model. In the second stage, the best-fit solution from the first stage was used as initial values and the calibration against the same experimental data from Sgouralis et al (58) was continued until the best-fit solution for the bolus model was found.

Fig. 4. Comparison of bladder-urine PO_2 in rabbit predicted by CF and bolus models against experimental data from Ref (58) after model calibration. Panel A: saline with PO_2 of 2 mmHg (after bubbling with pure nitrogen) initially infused at the proximal ureter. Panel B: saline with PO_2 of 111 mmHg (after bubbling with nitrogen containing 12% oxygen) infused at the proximal ureter. Panel C: saline with a PO_2 of 159 mmHg (after bubbling with air containing 21% oxygen) infused at the proximal ureter. The solid lines represent measured values, the dashed lines represent the predictions of the CF model, and the dotted lines represent the predictions of the bolus model. The error bars with small cap represent ± 1 SEM, and large caps represent ± 2 SEM.

Fig. 5. Comparison of rate of change in bolus urine PO_2 in human under different initial conditions. Panel A: Rate of change in urine bolus PO_2 with various values of initial pelvic-urine PO_2 (arterial PO_2 (P_aO_2) = 90 mmHg and urine flow (UF) = 0.6 ml/min/ureter). Panel B: Rate of change in urine bolus PO_2 with various values of P_aO2 (initial pelvic-urine PO_2 = 0 mmHg and UF = 0.6 ml/min/ureter). Panel C: Rate of change in urine bolus PO_2 with various values of UF (initial pelvic-urine PO_2 = 0 mmHg and P_aO_2 = 90 mmHg). Panel D: Rate of change in urine bolus PO_2 with various values of PF (peristaltic frequency; initial pelvic-

urine PO_2 = 0 mmHg and P_aO2 = 90 mmHg). Solid lines in panels B, C and D represent baseline P_aO2 (90 mmHg) and UF (0.6 ml/min/ureter with PF of 3/min).

Fig. 6. Comparison of bladder-urine PO_2 in human with variations in bolus volume and peristaltic frequency. The graphs show the change in bladder-urine PO_2 with changes in either bolus volume (solid lines) or peristaltic frequency (dashed lines). The top axis refers to the change in urine flow with peristaltic frequency (dashed line) and a constant bolus volume (V_B = 0.2 ml). The bottom axis refers to the change in urine flow with bolus volume (solid line) and a constant peristaltic frequency (f_B = 3/min). For example, at the bottom axis, a bolus volume of 0.8 ml results in urine flow of 2.4 ml/min/ureter (0.8 ml × 3/min). At the top axis, a peristaltic frequency of 6/min results in urine flow of 1.2 ml/min/ureter (0.2 ml × 6/min). Urine flow ranges from 0.1 ml/min/ureter (urine volume = 0.033 ml, or frequency = 0.5/min) to 2.4 ml/min/ureter (urine volume = 0.8 ml, or frequency = 12/min). Panel A: Bladder-urine PO_2 for initial pelvic-urine PO_2 of 0 mmHg. Panel B: For initial pelvic-urine PO_2 of 10 mmHg. Panel C: For initial pelvic-urine PO_2 of 20 mmHg. (i), (ii), and (iii) next to the lines represent the arterial PO_2 ((i) = 90 mmHg, (ii) = 150 mmHg and (iii) = 300 mmHg).

Fig. 7. Relationship between pelvic-urine PO_2 and bladder-urine PO_2 in human for different initial bolus PO_2 condition. Panel A: P_aO_2 = 90 mmHg. Panel B: P_aO_2 = 150 mmHg. Panel C: P_aO_2 = 300 mmHg. UF = urine flow as a function of bolus volume. The pelvic-urine PO_2 is the initial bolus PO_2 as it enters the ureter, and the bladder-urine PO_2 is the final bolus PO_2 after transit time of 15 s. Note the bladder-urine PO_2 is the dependent variable in the model, but it is presented in the x-axis because the intended use of the model is to predict the pelvic-urine PO_2 based on the measured bladder-urine PO_2.

Fig. 8. Two-dimensional contour plot of urine flow, bladder-urine PO_2 and pelvic-urine PO_2 in human for two different levels of P_aO_2. Panel A: Under normoxic condition (P_aO_2 =

90 mmHg). Panel B: Under hyperoxic condition (P_aO_2 = 300 mmHg). Urine flow was determined assuming constant peristaltic frequency of 3/min. The bladder-urine PO_2 values are predicted for a transit time of 15 s.