Advective transport of nitric oxide in a mathematical model of the afferent arteriole

Kayne M. Smith, Leon C. Moore, and Harold E. Layton

1Department of Mathematics, Duke University, Durham, North Carolina 27708-0320; and 2Department of Physiology and Biophysics, State University of New York, Stony Brook, New York 11794-8661

Submitted 13 April 2002; accepted in final form 2 January 2003

Smith, Kayne M., Leon C. Moore, and Harold E. Layton. Advective transport of nitric oxide in a mathematical model of the afferent arteriole. Am J Physiol Renal Physiol 284: F1080–F1096, 2003.—Endothelium-derived nitric oxide (NO) is thought to be short-lived in blood because of rapid removal from plasma, mainly by binding to Hb. The extent to which removal limits NO advection is unclear, especially for blood flow in the renal afferent arteriole (AA), which has a transit time of 3–30 ms. A mathematical model of AA fluid dynamics and myogenic response that includes NO diffusion, advection, degradation, and vasorelaxant action was used to estimate NO advective transport. Model simulations indicate that advective transport of locally produced NO is sufficient to yield physiologically significant NO concentrations along much of the AA. Advective transport is insensitive to NO scavenging by Hb because the NO-Hb binding rate is slow relative to AA transit time. Hence, plasma NO concentration near the vessel wall is influenced by both diffusion from endothelial cells and advection from upstream sites. Simulations also suggest that NO advection may constitute a mechanism to stabilize arteriolar flow in response to a localized vasoconstriction accompanied by enhanced NO release.

kidney; renal hemodynamics; myogenic mechanism; immersed boundary method

Endothelium-derived nitric oxide (NO) is an important regulator of renal microvascular tone. NO is a mediator of the vasorelaxant effects of several agents, including acetylcholine and bradykinin (27), and NO modulates the effects of several vasoconstrictors, including endothelin and ANG II (11, 35). As a consequence of its action to desensitize vascular smooth muscle (VSM), NO also modulates the myogenic reactivity of the preglomerular vasculature. Myogenic reactivity, an intrinsic property of arterial vessels to constrict in response to increased intravascular pressure, plays a major role in the autoregulation of renal blood flow and glomerular filtration rate (9, 26).

Because of its small size, NO diffuses rapidly through most biological membranes and tissues, where it is consumed in various reactions. In particular, NO binds to Hb and other heme-containing proteins, it reacts with superoxide to form peroxinitrite radicals, and it forms S-nitroso (SNO) adducts on Hb and on other proteins (15, 32).

In the traditional paradigm, NO is a paracrine agent that affects myogenic reactivity by diffusing from endothelial cells (EC) to neighboring VSM cells, where it influences a variety of cellular functions (27). In contrast, the fate of NO released from EC into the vascular lumen is less clear. Initially, it was thought that such NO would diffuse into the bloodstream and rapidly bind with Hb; as a consequence, free NO levels in plasma would be very low (20), and NO transport in blood by means of axial advection1 would be of little physiological significance. This view has been challenged in recent years. The reaction that forms nitrosothiol residues on Hb and albumin is reversible, and that reversibility provides a mechanism for NO transport over long distances (15). Furthermore, after NO is released from the endothelium, four stages of diffusion are required for NO to reach Hb in a red blood cell (RBC): diffusion through blood plasma from the endothelium to the central lumen (where most RBC are suspended), diffusion to the RBC membrane, diffusion across the RBC membrane, and diffusion within the RBC cytoplasm to reach Hb. Detailed experimental and mathematical analyses of these transport processes suggest that the NO scavenging rate in flowing blood is about three orders of magnitude lower than previously believed (37, 38).

One factor that slows the scavenging of NO in the vascular lumen is the surprisingly low NO permeability of the RBC plasma membrane, which was recently estimated to be ~2,000 times less than the NO permeability of a pure lipid membrane (38). Another factor that may limit NO scavenging, and a focus of this investigation, is the diffusion resistance presented by the (nearly) RBC-free boundary layer adjacent to the endothelium. Evidence for such resistance to NO diffusion comes from experiments that show that intra-

1 In this context, “advection” denotes the motion of fluid, or transport of solute by fluid motion, along the tubular lumen; “axial” indicates the long axis of the AA, the axis that coincides with the blood flow direction. In subsequent usage, advection is assumed to be axial.

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vascular flow reduces NO consumption by RBC but does not affect NO consumption by free Hb, implying that NO consumption is reduced by the RBC-free zone present in flowing blood (21). The physical basis for diffusion resistance in the boundary layer has been thought to be NO accumulation in the layer via diffusion from the EC, resulting in boundary layer NO levels higher than in VSM and in local concentration gradients that favor net transport from the EC to the VSM cells (21).

In a renal afferent arteriole (AA), the presence of such high NO concentration in the RBC-free plasma layer suggests that significant NO may be advected in that layer, because the layer is sufficiently thick (~2 μm) (4) to have an average flow velocity that is a substantial fraction of whole AA average flow velocity. If so, NO advection in the boundary layer could substantially increase the axial distance over which locally produced NO influences vascular tone, as well as contribute to the development of the diffusion resistance in the boundary layer. This possibility has not been previously analyzed in model studies (5, 20, 39, 41, 45), probably because detailed modeling of transport dynamics involves formidable difficulties. A detailed model requires a representation of fluid dynamics, coupled with NO diffusion and advection, within walls having a configuration that is determined, in part, by local physical factors and NO concentration.

The objective of this study was to investigate the influence of advective NO transport in the plasma boundary layer on the distribution of NO in an AA. To accomplish this, we used a previously developed mathematical model of solute diffusion and advection in an AA to predict the fate of NO released from the vascular wall. The model simulations suggest that advection of locally produced NO is of sufficient magnitude, relative to the NO degradation rate, to influence vascular tone substantial distances downstream from the release site. Furthermore, simulations suggest that such axial NO transport may serve to stabilize segmental blood flow in response to local constriction and/or injury in the proximal AA.

MATHEMATICAL MODEL

An analysis of NO transport in an AA requires an approximation of the flow field within a region having dimensions and pressures similar to those in an AA; a representation of the impact of myogenic reactivity, including its modulation by NO, on AA diameter; and a simulation of the transport and metabolism of NO. The model AA used in this study, which was previously developed and tested (2), consists of three analogous components. The first component is a representation of the AA wall, the fluid motion and pressure within the AA wall, and the motion of the AA wall in response to fluid pressure and myogenic forces. The second component consists of myogenic submodels, which are elastic-contractile elements that represent the spatially distributed myogenic force generated in response to intraluminal pressure; these submodels modulate the myogenic force as a function of local NO concentration. The third component is a representation of NO release, binding, degradation, and transport (by both diffusion and advection) in the model AA lumen and in nearby surrounding tissue.

AA Model Configuration

The full mathematical model (AA model) represents incompressible fluid flow through a two-dimensional channel. That channel represents the AA lumen, the channel boundary represents the arteriolar wall, and the channel flow is considered to consist of blood plasma and blood cells. To incorporate the dynamics of the interaction of channel flow (i.e., blood flow) with the channel boundary (i.e., arteriolar wall), the model employs the immersed boundary method (29, 30). A two-dimensional flow channel was used because the immersed boundary method is more readily formulated in rectangular coordinates than in cylindrical coordinates and because a three-dimensional formulation would require prohibitive numerical computational times. The use of a two-dimensional channel rather than a cylindrically axisymmetric configuration introduces a systematic bias, in that flow velocities computed in a channel exceed those in a cylinder, given the same pressure gradient. However, relative to the normal variations in length, diameter, and flow in a population of afferent arterioles, this bias is not large (see DISCUSSION). Our model arteriole was formulated so that pressure profiles in its flow channel are in good agreement with physiological measurements (see Figs. 3 and 5 and associated text).

The forces exerted on the fluid by the channel boundary are computed by means of a phenomenological model that provides the relationship between intravascular pressure and the myogenic response, a response that is modulated by NO concentrations at the channel boundary. That phenomenological model, the myogenic response model, or, simply, "myogenic model," is a subcomponent of the AA model: the AA model includes hundreds of myogenic model elements (see below).

The AA model is illustrated in Fig. 1. In the bottom section of the figure, the model arteriole wall (labeled W) is contained within a rectangular fluid domain. A fluid source (shaded square) is situated near the left end of the model AA, and a corresponding sink is near the right end; an arrow indicates flow direction. The flow rate can be adjusted by varying upstream and downstream pressures and resistances, that is, an upstream pressure that is separated from the source by a resistance and a corresponding downstream pressure that is separated from the sink by a resistance (resistances are not illustrated). To minimize the influence of end effects (arising from the source or sink) on model interpretation, most figures showing results will include only the interior region between the vertical gray lines, i.e., the region between x = 0 and x = 140 μm.

For some simulations, we computed AA blood flow; the calculation involved two steps. First, flow was calculated for a channel having a reference "height" of
100 μm (height indicates distance along the z-axis, which is perpendicular to the plane that contains the vessel walls illustrated in Fig. 1); this calculation, which corresponds to Eq. 8 in Ref. 2, was based on the pressure drop across the upstream resistance that is external to the model vessel. In the second step, flow through a cylindrical vessel was estimated by scalings that incorporated the vessel diameter and its presumed circular cross section: the value obtained from the first step was multiplied by $D/(100 \mu m)$, where $D$ was the average model AA diameter, to represent flow through a square cross section with side $D$, and that result was multiplied by $\pi/4$ to produce a rectangular cross section with an area equivalent to a circle having diameter $D$. The scaling of the channel flow by a factor of $D$ preserves the proportionality of flow to the fourth power of diameter that is characteristic of cylindrically axisymmetric flow.

The top portion of Fig. 1 is a schematic enlargement of a portion of the model AA. The AA wall is constructed of nodes [material points in the fluid (● in the figure)] that are connected by elastic or elastic-contractile elements. Along the AA wall, the nodes are linked by elastic elements (essentially passive springs with fixed rest lengths). Across the wall (i.e., transverse to the flow direction), the nodes are connected by elastic-contractile elements that make up the myogenic element; each element is composed of an active spring, of variable strength $K_M$, configured in parallel with a dashpot that is characterized by damping coefficient $\gamma$ (see expanded element in Fig. 1, top right). As the model walls move within the fluid, and as the myogenic response is activated (through $K_M$) in the myogenic model, the elastic and elastic-contractile elements exert forces on the nodes, and the nodes, via the immersed boundary method, exert a force density, localized along the AA wall, on the fluid domain.

Myogenic Response Model

The myogenic model includes both steady-state and transient responses (2). The myogenic force applied to the boundary nodes by the model is a function of intravascular pressure, elapsed time, vessel diameter, rate of change of vessel diameter with respect to time, and local NO concentration. The parameter values for the myogenic model were obtained by fitting the model to myogenic responses obtained in vitro from blood-perfused rat juxtamedullary AA. The AA were subjected to approximate step-changes in perfusion pressure (from 60 to 100 mmHg) with a transition time constant of ~1.1 s; resulting changes in vessel diameter were determined from video recordings using methods described in Ref. 8. The measured autoregulatory responses included contributions from both the myogenic and tubuloglomerular feedback (TGF) mechanisms. Thus the strength of the myogenic response, as determined by the fitting, is sufficiently high to include the contribution of the TGF mechanism, which is not explicitly represented in our model. The experimental response and our model fit are illustrated in Fig. 2. The AA model myogenic response magnitude and time course are similar to those shown for both the experimental response and the response of a single myogenic element.

To compensate for the decline in intravascular pressure along the AA segment, a spatial inhomogeneity was incorporated into the strength of the myogenic model elements (2). Without this inhomogeneity, the diameter of the model AA increased as luminal pressure decreased along the length of the model AA, whereas AA in vivo have diameters that are relatively uniform along the length of the arteriole (see Fig. 5).

Figure 3 illustrates the capability of the full AA model to autoregulate flow as feed pressure increases. The dashed lines show steady-state results obtained...
without myogenic reactivity: the model vessel dilates passively, and both flow and outflow pressure increase. With the myogenic response activated (solid lines), the vessel constricts as feed pressure increases, and blood flow and outflow pressure are stabilized. The predicted steady-state autoregulation responses are in reasonable agreement with experimental measurements (7, 8).

**Modeling NO Transport, Removal, and Vasorelaxant Effect**

NO is released from the arteriolar walls, advects with the local fluid velocity, diffuses, and degrades as a function of time and location within the model arteriole. NO can also diffuse into the region outside the vessel; that region represents the interstitium and tissues surrounding the arteriole.

As is generally characteristic of flowing blood, we assume that the hematocrit will be highest at the AA center and essentially zero near the vessel wall (10). Thus to represent the spatial distribution of NO binding to Hb and of the loss of NO in reactions with superoxide and sulfhydryl residues on Hb, the rate of NO removal from the model fluid was scaled by a decreasing function of distance from the center axis $y = 0$ of the model AA. Specifically, the removal rate was scaled through multiplication by a curve obtained from a symmetrical pair of hyperbolic tangent functions, as illustrated in Fig. 12A; the distance from the vessel wall to the inflection point of the rise varied locally and dynamically along the vessel as vessel diameter changed.

NO-mediated VSM relaxation was represented by making the myogenic response strength, $K_M$, a function of local NO concentration (2); the response was scaled in accordance with a dose-response curve relating NO concentration to rat aorta diameter (16), resulting in a curve that related NO concentration to the percentage of myogenic relaxation (see Fig. 4).

Basal NO release was not represented explicitly in the model AA; instead, basal NO release was implicitly incorporated by assuming that the model configuration was determined, in part, by basal NO release and that the configuration therefore included the effects of basal NO release. Because this investigation principally involves a hypothesis about the effects of advection and diffusion on NO distribution, it should be sufficient for most purposes to determine the fate of a representative increment of NO release from a localized site. However,
in one simulation a low, uniformly distributed NO release rate was introduced to ascertain the likely effect of advection on diffusion resistance all along the AA (see Fig. 13). The NO distribution so obtained should be indicative of the distribution of basally released NO, provided that basal release is uniformly distributed along the vessel wall.

**Model Parameters**

AA model dimensions, used in all simulations, were chosen to be similar to those observed in short juxtamedullary AA (6). We chose to represent a relatively short AA (140 μm, excepting the distal segment) to reduce the computational time required to solve the model (see below); we chose a target diameter of 16 μm. We did not represent the most distal segment of the arteriole, which is the principal effector site of TGF and which, in juxtamedullary AA, tapers by ~25% in diameter.

Model parameters, summarized in Table 1, characterized the fluid, the fluid pressures at the source and sink, and the release, diffusion, and removal of NO. We specified a set of parameters that yielded a “base-case” steady-state solution to the AA model, assuming no NO release above the basal rate. In addition, we specified a “standard” release rate for incremental NO release above the basal rate, a standard that we used for comparisons and parameter studies. Along with that standard rate, we assumed a base-case parameter to characterize NO binding, a base-case configuration for the spatial distribution of Hb (see above), and a base-case dose-response curve for the vasorelaxant effect of NO (Fig. 4).

To keep the problem tractable, blood was simulated as a Newtonian fluid of uniform density 1.055 gm/cm³ (1) and with an apparent dynamic viscosity of 1.75 × 10⁻² g·cm⁻¹·s⁻¹, based on measurements in an arteriole (with a diameter of 23 μm) from cat mesentery (22). The pressures and fixed resistances at the source and sink were chosen so that the base-case pressures at the fluid source and sink, 95 and 50 mmHg, respectively, would be consistent with pressures found in rat juxtamedullary AA (8).

We used a standard NO release rate of 3.275 × 10⁻¹⁵ mol·μm⁻²·s⁻¹; this rate should be interpreted as the increment of elevation above the basal base-case NO release rate (see above) from the luminal AA wall. This rate is more than an order of magnitude smaller than the NO release rate of 5.2 × 10⁻¹⁴ mol·μm⁻²·s⁻¹ estimated for rabbit aorta (39).

NO diffusivity has been measured to be 3.3 × 10⁻⁵ cm²/s at 37°C in rabbit aorta (24), a value consistent with rapid diffusion in aqueous solutions. We assumed that NO diffuses readily across the plasma membranes of EC and VSM cells (24). The base-case half-life for NO, taken as constant throughout the fluid domain, represents the removal of NO due to binding with substances found outside the lumen; it is based on a measured half-life of ~1 s for NO in blood-free perfused guinea pig heart determined in Ref. 3 from data in Ref. 17. Within the lumen, NO is removed at a much faster rate; the base-case rate of NO-Hb binding, which corresponds to a half-life of 20 ms, is based on the determination that <100 ms are required for complete reaction of HbO₂ with NO (16).

**Numerical Calculations**

The immersed boundary method, which was used to simulate the interaction between the fluid and the boundary (i.e., AA wall), uses a Lagrangian² representation for the boundary; the boundary is coupled by approximate Dirac delta functions to an Eulerian grid, on which the fluid calculations are conducted (29). The

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Table 1. **Model parameters**

<table>
<thead>
<tr>
<th>Description</th>
<th>Dimensional Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid density</td>
<td>1.055 g/cm³</td>
</tr>
<tr>
<td>Apparent dynamic blood viscosity</td>
<td>1.75 × 10⁻² g·cm⁻¹·s⁻¹</td>
</tr>
<tr>
<td>Resistance upstream from fluid source</td>
<td>100 mmHg</td>
</tr>
<tr>
<td>Resistance downstream from fluid sink</td>
<td>8 × 10⁷ g·cm⁻¹·s⁻¹</td>
</tr>
<tr>
<td>Downstream external pressure</td>
<td>0 mmHg</td>
</tr>
<tr>
<td>NO release rate, standard</td>
<td>3.275 × 10⁻¹⁵ mol·μm⁻²·s⁻¹</td>
</tr>
<tr>
<td>NO diffusivity</td>
<td>3.3 × 10⁻⁵ cm²/s</td>
</tr>
<tr>
<td>NO half-life</td>
<td>1 s</td>
</tr>
<tr>
<td>NO-Hb half-life, base-case</td>
<td>0.02 s</td>
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</table>

NO, nitric oxide. Resistances assume flow in a channel having a height of 100 μm.

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²In the Lagrangian representation, boundary nodes are advected in time at the local fluid velocity, and these nodes take positions that need not coincide with the points of a fixed numerical grid; moreover, in a Lagrangian representation, events are observed from the reference frame of the moving nodes. In contrast, the Eulerian representation corresponds to quantities defined on a regular Cartesian grid that remains fixed in time, and events are observed from the reference frame of that fixed grid. The approximate Dirac delta function is a bell-shaped weighting function that is only locally nonzero and that acts to distribute a quantity from a node to nearby fixed grid points or from a fixed grid point to nearby nodes.

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Fig. 4. **Dose-response curve for nitric oxide (NO) based on data from Ref. 16. Percent relaxation is presented as a function of AA wall NO concentration: 0% relaxation corresponds to fully myogenic (active) behavior; 100% relaxation corresponds to fully passive behavior (see Fig. 3).**
procedure for advancing one time step (2) involves the following steps. 1) From the elastic and elastic-contractile elements, determine the force density (force per unit volume) on the boundary nodes and transfer that density, via approximate delta functions, to the Eulerian grid. 2) Solve the incompressible Navier-Stokes equations for the fluid velocity and pressure throughout the fluid domain; include terms in these equations for the pressure source, the pressure sink, and the force density arising from the immersed boundary. 3) Solve the equations for solute advection and diffusion, with source terms for NO release and degradation, to obtain the concentration of NO throughout the fluid domain. 4) Transfer the fluid velocity from the Eulerian grid to the nodes that make up the Lagrangian boundary by means of approximate delta functions; then, advect the boundary at the local fluid velocity.

Because we previously demonstrated that a spatial resolution of 1 µm or less is needed to track fluid and solute motion with sufficient accuracy for physiologically meaningful simulations (2), a spatial grid of 128 × 512 subintervals was used, resulting in a discretization step of h = 1/512 × 0.02 cm (0.390625 µm). The model arteriolar wall was constructed of 1,920 nodes, connected by 1,920 elastic springs; 865 node pairs were connected by transverse elastic-contractile myogenic elements (the 190 nodes without transverse connections enclose the ends of the model vessel).

Although some of the numerical techniques used for solving the AA model are implicit and thus do not restrict the numerical time step, others are explicit (because we know of no practical alternatives) and therefore require a small time step, relative to key physiological time scales that are relevant to our study. In particular, a numerical time step of ~0.3 µs is required to solve the full AA model, and, consequently, ~315 h of computational time are required for 0.1 s of elapsed model time on a desktop computer equipped with a 1-GHz CPU and 256 MB of RAM. Because the full myogenic response in vivo requires ~10 s, a time-scale adjustment was introduced to make model simulations practical: the speed of the simulated myogenic response was increased by a factor of 175 relative to in vivo responses.

The adjusted time scale allows us to closely approximate steady-state model solutions (absolute steady states cannot be attained because the final phase of the approach to a steady state, which involves only small changes, is slow). Moreover, depending on the object of one’s investigation, the change of scale may not significantly affect dynamic simulation results. For example, the fluid transit time through the model arteriole (~4 ms) is much faster than the characteristic time of the myogenic response, whether a comparison is made with the in vivo response (~10 s) or the response in the accelerated time-scale, which is ~60 ms. Thus even with the adjusted time scale, the accelerated myogenic response acts on a time scale that exceeds the AA transit time by more than an order of magnitude. Because the intravessel information is renewed rapidly relative to the myogenic response, the dynamic behavior of the AA model may still approximate qualitative in vivo behavior, although accelerated by more than two orders of magnitude.

Model Verification

Although the model framework used in this study was previously tested (2), significant changes were made in several of the model parameters to more closely simulate AA dimensions and flows. Hence, for the base-case parameters used in this new study (but with no elevated NO release), we verified that fundamental characteristics of the model still agree well with expected behaviors. These tests are summarized in Figs. 5–8.

Figure 5 shows the diameter, average velocity, and pressure along the length of the model AA for the case of increasing (i.e., inhomogeneous) myogenic response (solid curves) as a function of distance x and for the
case of spatially uniform (i.e., homogeneous) myogenic response (dashed curves). The average velocity is computed across the diameter of the model vessel by dividing the planar flow rate by the diameter; the pressure is measured along the centerline of the AA flow, i.e., along the line $y = 0$. One should recall that the diameter is determined by the local intravascular pressures and by the myogenic response characteristics, which vary with position. For the case of inhomogeneous myogenic response (which is the base-case configuration), the diameter and average velocity vary somewhat along the model vessel, although less than for the

![Image](Fig. 6. Base-case pressure as a function of position on fluid domain. Intersections on wireframe diagram correspond to every 4th discretization value along axes of computational grid.)

![Image](Fig. 7. Comparison of simulated velocity and shear stress profiles with profiles for planar Poiseuille flow. A: velocity profiles. Solid line, fluid velocity profile along y-axis computed by AA model at the cross section where $x$ = 70 μm; dots, computational grid locations. Velocity profiles for Poiseuille flow are shown for 3 diameters: diameter $D$ of model AA based on node locations, $D - 2h$, and $D - 4h$, where $h$ is the numerical grid subinterval. Horizontally striped boxes above profiles show locations of boundary nodes (heavy lines) and the wall thicknesses (in $h$-increments), based on extent of approximate delta functions. B: shear stress profiles. Solid line, shear stress calculated from local pressure gradient computed by AA model; dashed line, shear stress for Poiseuille flow based on diameter $D$; vertical bars, extent of approximate delta functions that form AA wall boundary (total width is $4h$); first 3 values at top right: analytical shear stress magnitudes at wall center (based on node locations), at the interior edge of the wall with thickness $2h$ (light gray sections of vertical bars), and at interior edge of the wall with thickness $4h$ (full vertical bars), respectively; last value at top right is maximum shear stress magnitude computed by model across model AA lumen.)
homogeneous response case, and the decrease in pressure is more nearly linear than for the homogeneous case. For the homogeneous myogenic response, the progressive dilation of the AA is a consequence of the myogenic response as intravascular pressure decreases; the dilation results in an average velocity that is decreasing and in pressure with a decreasing slope magnitude. Figure 5 illustrates two points: the base-case vessel, with inhomogeneous myogenic response, maintains a diameter that is within 6.5% of the target diameter, and therefore the diameter appears nearly uniform; and, as we pointed out in Ref. 2, in vivo the AA must provide an inhomogeneous myogenic response to maintain a nearly uniform diameter in the presence of decreasing intravascular pressure.

Figure 6 shows pressure as a function of position on the entire fluid domain for the base case (cf. Fig. 1). The fluid source and sink are manifest as local pressure deviations at each end of the model arteriole. Away from the source and sink, and at each cross section (i.e., at each fixed $x$), the pressure is nearly constant in the intravascular region and (with a different constant) outside the vessel wall. Along the flow direction the pressure decreases nearly linearly inside the model vessel. The grid line that curves substantially along the side of the tubular wall is a consequence of the small change in diameter indicated by the solid line in Fig. 5A. Figure 6 demonstrates that the pressure distribution behaves as expected for Poiseuille flow inside the model vessel and, indeed, throughout the fluid domain.

Figure 7A compares the simulated fluid velocity profile (solid line) along the cross section at $x = 70 \, \mu m$ with exact velocity profiles for planar Poiseuille flow. Excellent agreement was found between the simulated profile and the (exact) Poiseuille flow profile, when that flow profile was based on the local pressure gradient and on the diameter $D - 2h$, where $D$ is the diameter that corresponds to the distance between the centers of the opposing nodes in the model vessel walls, and $h$ is the spatial discretization distance in the numerical method. Because of the spatially distributed approximate delta function used by the immersed boundary method, the exact width of the model wall is not prescribed a priori but arises from the interactions of the components of the numerical method. However, the investigation in Ref. 2 indicated a wall width of $2h$. 

Fig. 8. Advection of solute bolus in steady-state flow. Dashed yellow lines, centers of vessel walls; bar at right, concentration scale (C; in $\mu M$). Topmost panel corresponds to $t = 0$; each successive panel is time-advanced by 0.45 ms. At $t = 0$, the bolus has a 2-dimensional Gaussian distribution; in successive panels, the bolus is deformed by the nearly parabolic velocity profiles of approximate Poiseuille flow.
which is consistent with the effective diameter found here.

Figure 7B compares the magnitude of the simulated shear stress profile (solid line) with the magnitude of the (exact) Poiseuille shear stress profile (dashed line), based on the local pressure gradient. The shear stress was computed, in both cases, along the same cross section used in the calculation of the velocity profile. The width of the nodes that make up the boundary wall, $4h$, is indicated by the vertical gray bars; the more lightly shaded inner portion of the bar has width $2h$. As can be seen in the figure, excellent agreement was found up to the interior edge of the walls. The simulated shear stress decreases to near zero as it passes through the layer containing the approximate delta functions.

The advection of NO is illustrated in Fig. 8. In this test, NO diffusion, NO binding/degradation, and myogenic reactivity were disabled, and a simulated bolus of NO, distributed as a two-dimensional Gaussian, was placed near the source end of the model vessel and allowed to advect with the fluid. Each successive frame is time-advanced by 0.45 ms. The parabolic shape of the expected planar Poiseuille flow is easily seen as are substantial amounts of NO that remain near the walls of the model arteriole within the boundary layer near the initial location of the bolus. The nearly stationary solute in the boundary layer illustrates that the model flow has essentially zero velocity at the vessel wall.

RESULTS

NO Transport in the Boundary Layer

To estimate the extent of NO transport within the RBC-free boundary layer, NO was released from the wall at a site near the beginning of the model vessel. Thus at $t = 0$, NO was released from both sides of the AA model channel at the standard rate (as characterized in MATHEMATICAL MODEL) of $3.275 \times 10^{-15}$ mol·μm·s$^{-1}$; the release sites, centered at $x = 19.2$ μm, were 8.2 μm long. The initial vessel diameter and intravascular pressure profile were those given by the base case (shown as Inhomogeneous in Fig. 5). The resulting advective-diffusive transport of NO is illustrated in Fig. 9; the topmost panel corresponds to $t = 0.3$ ms, and each successive panel is time-advanced by 0.9 ms. The vessel boundary is indicated by dashes.

In the first millisecond, the results show rapid diffusion of NO into the abluminal space occupied in vivo by VSM cells. In the model AA, where the myogenic response time of the VSM has been accelerated, a local dilation occurs around the release site. NO also diffuses into the lumen, where it is advected by the fluid stream. With increasing time, NO diffuses further into the abluminal space and is transported further down the vessel, leading to additional downstream vasodilation. The intravascular NO concentration downstream from the release site is highest just within the vessel, but not at the vessel wall, a pattern that reflects the essentially zero fluid velocity at the wall. Downstream from the release site, NO diffuses from the boundary layer toward the wall and into the abluminal compartment. Direct diffusion from the release site cannot account for the NO in that compartment so far downstream, because the distances are much greater than the diffusional spread into the abluminal space in the direction perpendicular to the $x$-axis of the model vessel.

This point is illustrated in Fig. 10, which shows the concentration profiles along the line that is centered at the release site and is perpendicular to the flow axis of the vessel. Profiles for three time points after the onset of release are shown: 3, 6, and 9 ms. (At the onset of release, the NO concentration arising from incremental NO release is 0 throughout the fluid domain; i.e., at the onset of release, NO release is at the basal rate.) Two points are noteworthy. First, at 9 ms, the distance that NO diffuses significantly (at a concentration of at least 0.005 μM) into the abluminal space is 5–6 μm, a much smaller distance than the axial distance NO is advected down the vessel (30 μm). Second, within the lumen, the NO concentration is lowest at the center axis ($y = 0$) of the vessel, owing to the continuous arrival of fluid with low basal NO content. This low concentration results in a steep concentration gradient directed from the wall into the lumen, a gradient that persists well downstream as NO enters the flowing fluid and is bound or degraded. Unless NO diffusivity through the luminal EC plasma membrane differs significantly from the diffusivity through the abluminal EC plasma membrane, the asymmetry in the diffusion gradients will drive the majority of locally released NO into the lumen. This result shows that advective NO transport has a substantial effect on the distribution of NO. (The NO concentration near the center axis of the vessel is also suppressed by NO-Hb binding; see below.)

Sensitivity Studies

Figure 11 shows results from three simulations in which the NO release rate was varied by two orders of magnitude: the standard rate multiplied by 0.10, 1.0, and 10. For the configuration in which NO was locally released (Fig. 9), Fig. 11 shows NO concentration profiles along the wall of the vessel at 9 ms after the onset of NO release. As expected, NO concentration varied directly with the release rate, whereas the shape of the profile changed little. NO release rate and tissue sensitivity to NO are related, in that increases in either factor will extend the distance over which the released NO will influence local vascular tone, whereas reciprocal changes (of similar magnitudes) in these parameters should have little effect.

Figure 12, A and B, illustrates sensitivity to the effective width of the RBC-free zone in the boundary layer. Figure 12A shows four different spatial distributions of NO-Hb binding that vary the cell-free zone from 0 to 25% of AA diameter. The four curves in Fig. 12B, which are nearly superimposed, correspond to the differing distributions of NO-Hb binding shown in Fig. 12A. At the base-case binding rate, changes in the
effective width of the cell-free zone had almost no effect on the NO concentration profile. In part, the insensitivity of the distribution of NO to the width of the RBC-free layer results from a base-case removal rate (i.e., a reaction velocity) that is small compared with AA blood flow velocity.

Figure 12C shows surprising effects of NO-Hb binding within the lumen: aside from small changes in the magnitude of the peak at the release site, neither a complete elimination of NO-Hb binding nor a constant distribution of NO-Hb binding within the domain had a major effect on NO distribution along the vessel. To estimate the NO-Hb binding rate that might be required to markedly reduce NO concentration, the binding rate was increased from the base-case value by one and two orders of magnitude. The results suggest that a 100-fold increase in the removal rate is needed to reduce the magnitude of the peak by \( \sim 50\% \), whereas a 10-fold increase significantly reduces NO concentrations downstream from the release site.

**Effect of Distributed NO Release**

The foregoing results appear to suggest that the thickness of the boundary layer and the NO removal rate have little influence on the distribution of NO...
along the arteriole. However, in these simulations of localized incremental NO release, steep NO concentration gradients are established between the site of release and the lumen upstream from the release site; therefore, the arriving fluid presents little resistance to the diffusion of NO into the lumen. To investigate the establishment and impact of NO accumulation in the boundary layer, as might occur during basal NO release, additional simulations were conducted where the incremental NO release was distributed along the vessel wall. Figure 13 shows the results of a simulation with uniform NO release from $x = 12$ to $x = 127$ μm. To simulate a very small increment in basal NO release, the release rate was reduced to 0.01 the standard rate. (Note that the scaling of the concentration key in Fig. 13 differs from that in previous figures.)

![Figure 10](image1.png)

**Fig. 10.** NO concentration cross section from model AA at $x = 19.2$ μm for simulation illustrated in Fig. 9. Lumen of model AA is indicated by gray bar. Concentration profiles for 3 time points after onset of release are shown: 3 (solid line), 6 (gray line), and 9 ms (dashed line). Fourth panel from top in Fig. 9 corresponds to $t = 3$ ms.

![Figure 11](image2.png)

**Fig. 11.** Sensitivity of wall NO concentration to NO release rate. NO concentration measured along model AA wall at 9 ms after initial release for indicated factors of standard NO release rate is shown. In each simulation, NO was released from 8.2-μm model AA wall segments centered at $x = 19.2$ μm.

![Figure 12](image3.png)

**Fig. 12.** Sensitivity of NO distribution to location and magnitude of NO-Hb binding. A: relative strength of binding coefficient across AA model cross section. At each spatial location, NO-Hb binding rate is product of NO-Hb binding coefficient and a multiple of base-case NO-Hb binding rate. The binding coefficient curve is a function of wall location in space and time; as diameter decreases, so does relative size of nonzero region; $D$ corresponds to local diameter of model AA, whereas $D/2$ corresponds to model AA wall locations; solid curve, base-case NO-Hb binding coefficient curve used in most simulations. The 3 other curves correspond to parameter studies illustrated in B. B: sensitivity of AA wall NO concentration to NO-Hb binding coefficient. At $t = 0$, NO was released at standard release rate from 8.2-μm model AA wall segments centered at $x = 19.2$ μm. NO concentration along model AA wall at 9 ms of elapsed time for 4 NO-Hb binding coefficient curves from A was computed. The concentration profiles are nearly insensitive to differing binding coefficient curves. C: sensitivity of AA wall NO concentration to variation in NO-Hb binding rate in NO release experiments analogous to those in B using base-case NO-Hb binding coefficient curve (A, solid line). Solid curve, binding at base-case rate, which corresponds to binding half-life of 0.02 s; short dashed line, NO-Hb binding rate 10 times base-case rate; long dashed line, NO-Hb binding rate 100 times base-case rate. For comparison, simulation without NO-Hb removal (NO-Hb binding coefficient equals 0 everywhere) is shown by medium dashed line, and simulation with constant NO-Hb binding (NO-Hb binding coefficient equal to 1 everywhere) is shown by gray line.
simulations of localized release, the steep concentration gradients at the proximal end of the model AA favor NO diffusion into the lumen. As the blood moves along the AA, more NO diffuses into the boundary layer and its NO concentration rises. As this occurs, the NO gradient from EC into the lumen is progressively diminished, which establishes a diffusion resistance in the fluid adjacent to the vessel wall, as described by Vaughn et al. (40). The net result is enhanced diffusion from the EC into the tissue surrounding the distal AA where the highest tissue NO concentrations are established.

Response to Focal Vasoconstriction

Finally, simulation results suggest that NO release may stabilize segmental blood flow in response to a local vasoconstriction by reducing downstream vascular resistance. Increased shear stress at the site of vasoconstriction should result in a local increase in NO release (27). Furthermore, focal vascular injury is often associated with vasoconstriction and increased NO production; indeed, NO can be produced in large amounts by the inducible isoform of NO synthase (iNOS) at sites of vascular injury (14). If the vasoconstriction substantially reduced the intravascular pressure below normal, then a compensatory myogenic vasodilation would also occur and reinforce the vasorelaxant action of elevated NO levels.

To examine the potential role of NO, a focal constriction was simulated in the model AA, as illustrated in Fig. 14. After the gradual imposition, for ~30 ms, of a constriction centered at \(x = 19.2 \mu m\), NO was released at the standard rate on both sides of the AA model channel from 8.2- \(\mu m\) segments, also centered at \(x = 19.2 \mu m\). To distinguish between local and downstream effects, the constriction was maintained by making the myogenic elements in the constricted region insensitive to NO. The released NO was advected with the fluid and diffused: as it reached the model arteriolar walls, the walls relaxed, based on the base-case dose-response curve in Fig. 4. Figure 14 shows NO distribution along the model arteriole 30 ms after the onset of NO release: note the dilation downstream from the vasoconstriction. (One should recall that the myogenic response of the arteriolar wall was accelerated in these simulations.)

**Fig. 14.** NO distribution in constricted model AA 30 ms after initial release of NO. Dashed yellow lines, centers of vessel walls; bar, concentration scale (in mM).
Figure 15 provides a quantitative comparison of myogenic and NO-mediated compensation; Fig. 15A shows pressure profiles along the model AA, whereas Fig. 15, B and C, shows wall position and diameter, respectively. Four cases, at near steady state, are shown: 1) base-case (long dashed lines), which corresponds to the pressure profile (and diameter) before imposition of the constriction (as in Fig. 6); 2) constriction (thick gray line), which shows the effect of the constriction in the absence of either myogenic compensation or NO advection (this curve was constructed by using the spatially distributed vessel resistances from the constant flow rate, and then solving for the constant flow rate, and then solving for the pressure along the model AA using the constant flow rate and the resistance at each x); 3) constriction with myogenic compensation alone (constriction+myo; short dashed lines); and 4) the additional compensation provided by the advection of NO released at the site of constriction (constriction+myo+NO; solid line), as in Fig. 14. The percentage of base-case blood flow is given at the right of each pressure profile.

The constriction reduced flow through the model AA to 83% of base-case (430 nl/min) and increased the segmental resistance (pressure drop divided by flow rate) by 41% above base case. The effect of the myogenic response on the reduced downstream pressure results in a dilation along the remainder of the AA sufficient to return flow to 96% of its base-case value and to return the segmental resistance to 112% of its base case. Because we have employed a high myogenic gain to compensate for the absence of TGF, this degree of myogenic compensation is likely to exceed that achievable in vivo. When the effect of NO release is included, a further compensatory dilation occurs in the midportion of the vessel. The result is a further increase in outflow to 103% of the preconstriction value and a return to 100% of the preconstricted segmental resistance. These results illustrate the principle that advective transport of NO, together with downstream myogenic relaxation, may serve to stabilize segmental blood flow by reducing downstream vascular resistance in response to a focal constriction in the proximal AA.

It is noteworthy that in other simulations of this potential regulatory mechanism (not shown), the extent of compensation was highly dependent on the NO release rate from the constriction site, and compensation values well above and below 100% could be generated. This high sensitivity is a consequence of the feed-forward nature of this process as we have modeled it. However, in vivo, this autoregulatory mechanism would be embedded within the TGF system, and some degree of negative feedback control would be exerted. For example, if NO release from the site of constriction were insufficient to normalize AA flow, TGF would act to reduce AA resistance, thereby contributing to the restoration of normal flow. Conversely, if NO release were inappropriately high, TGF would act to restrain an increase in blood flow above normal.

DISCUSSION

The fate of NO released from EC and the extent of NO scavenging in the lumen of arterial vessels are issues that have generated much study and debate. A common notion is that free NO is short-lived: it is rapidly removed from the blood by binding to Hb, forming SNO adducts, or forming peroxinitrite. The consumption of NO in the vascular lumen is important, because rapid NO scavenging can greatly diminish diffusive delivery of NO to VSM cells.

We have used a mathematical model of fluid dynamics and solute transport in a renal afferent arteriole to assess NO advective transport to downstream VSM. Our model study extends the diffusive NO transport models developed by others (5, 20, 39, 41, 45). In each case, the fate of NO entering the lumen is an important factor, and the relative NO fluxes in the luminal and abluminal direction from the EC depend on the relative magnitude of the concentration gradients, under the assumption that EC membrane permeability is homogeneous. In these models, an important determinant of the intraluminal NO diffusion gradient, and thus NO distribution, is the rate of NO scavenging. However, our results suggest that advective transport of NO can also have a major impact on NO distribution.

Three interrelated findings arise from our study. First, model simulations predict that significant NO is advected in AA by the blood stream and that NO concentrations along the vascular wall are sufficiently large to influence downstream vascular tone as NO diffuses from the lumen into the vascular wall. Furthermore, advective NO transport is not limited to the RBC-free boundary layer. The second finding provides an explanation for the first: with physiologically reasonable rate coefficients, the luminal rate of NO-Hb binding is too slow, relative to the transit time of blood in a renal arteriole, to effect a major reduction in NO advection. Thus the principal determinants of NO concentration near the vascular wall are diffusive NO transport from adjacent EC into the lumen and advection of NO in blood plasma from upstream sites. The third finding, a consequence of the first two, is the potential for NO advection to stabilize arteriolar flow in response to a localized vasoconstriction associated with enhanced local NO release.

Model Limitations

Before discussing these findings, we examine the strengths and limitations of the complex model used in this study. By means of the immersed boundary method, detailed representations of fluid dynamics and resultant solute transport were obtained within and near a structure that exhibits dynamics similar to those of an AA. Specifically, the flow profile, shear stress rates, and diffusive and advective transport agree well with theoretical predictions. Furthermore, the AA model, which includes hundreds of embedded myogenic elements, exhibited autoregulatory behavior similar to that observed in vivo, suggesting that the
model provides a reasonable qualitative representation of an AA.

However, the AA model has some disadvantages and limitations in modeling arteriolar blood flow. First, the high velocities and steep pressure gradients characteristic of AA flow require high spatial resolution. This resolution, combined with the small time steps that are required to maintain numerical stability, resulted in long computational times. Owing to this, simulation times were limited to <1 s, an interval sufficient to establish key features of luminal advective transport of NO but insufficient to evaluate fully the extent of NO diffusion into the space external to the AA. In addition, we did not explicitly model structures in the extravascular space, such as VSM, that may scavenge NO at a rate higher than the base-case rate used external to the vessel (half-life, ~1 s).

A second limiting factor is that the immersed boundary method, to preserve computational tractability, was implemented in two-dimensional rectangular coordinates rather than in cylindrically axisymmetric coordinates, which would be more natural for a vessel's cylindrical geometry. Thus the model represents a channel of fluid with a width equal to the model arteriolar diameter and with an infinite extent in the $x$ direction, which is perpendicular to the $x$-$y$ plane of Fig. 1. Frictional forces are exerted on model AA flow only at the boundary of the channel, if the channel is considered to extend from the plane determined, e.g., by $z = 0$, to the plane $z = 16 \mu m$, then at the interface of the fluid at those planes, the interaction is frictionless.

A reasonable question is, To what extent do the flow velocities computed in our planar model differ from those that would be obtained in a model having cylindrically axisymmetric flow? An estimate of the difference can be obtained by comparing the velocity expression for Poiseuille flow (fully developed steady-state flow) through a cylinder with the corresponding expression for flow between parallel plates (i.e., a channel of infinite height). Let $D$ be the diameter of the cylinder or the diameter (i.e., width) of the channel used in this study, and let the length of the cylinder or channel be given by $L$. Then, in both cases, the explicit solutions to the Navier-Stokes equations show that flow velocities are proportional to $D^4/L$ (19). However, flow velocity in a cylinder is reduced, relative to a channel, by a factor of $\frac{1}{2}$, provided that the diameters, lengths, viscosity, and pressure drops are the same in the two configurations.

Although overestimation of flow velocity by a factor of two may seem to introduce significant error, our simulated flow velocities are not unreasonable when considered in the context of physiological flow velocity variation. For example, a maximal AA autoregulatory response to elevated perfusion pressure can reduce luminal diameter by ~30–40% relative to the diameter at the lower pressure limit of the autoregulatory range. With essentially constant blood flow, the mean flow velocity at the elevated pressure is increased two to three times over that at the lower pressure. Furthermore, with our base-case parameters, our planar channel has the same velocity profile (as a function of $y$), for example, as would arise in a cylinder (as a function of radius) with a diameter that is 25% larger than our base case and a length that is ~20% shorter (owing to the $D^4/L$ dependence). These variations in diameter and length are within the physiological range of dimensions reported for afferent arterioles (see below). Moreover, our fundamental conclusion that advection is an important mode of NO transport also depends on the value of NO half-life in the blood used in our simulations. In light of recent experimental studies (37, 38), the half-life value that we used may be substantially shorter than in vivo (perhaps by more than an order of magnitude). Hence, our fundamental conclusion is unlikely to be affected by the bias in model flow velocity introduced by the channel flow configuration.

Although we introduced a channel height scaling to ensure that flow is proportional to the fourth power of the diameter, as is the case in cylindrically axisymmetric Poiseuille flow (see Mathematical Model), the magnitude of the diameter changes needed to regulate flow in our planar model AA will exceed changes required by a cylindrical model, owing to the two frictionless sides of the channel. However, because the viscosity of blood in an AA in vivo is not constant, in that it tends to decrease with decreasing diameter (10), the inverse fourth-power relationship between diameter and segmental resistance is only approximate in the physiological setting. Indeed, the bias introduced by the channel configuration may counterbalance the bias arising from our assumption of spatially homogeneous viscosity.

Another potential limitation of our study is that we have not explicitly represented basal NO release, but, rather, we have represented a local increment of basal release. Because this increment is a small perturbation of the system, it should elicit a first-order accurate response that closely approximates a true response. This assumption avoids the complex issue of the interaction of incremental release with basal release, the inclusion of which would involve a formidable additional technical challenge. The parameters for our model AA (including pressure and diameter) and the parameters for the myogenic submodels were based on physiological measurements performed in intact AA under experimental conditions wherein normal basal NO release presumably occurred. For an explicit representation of basal release, a spatially distributed model for that release, including release stimulated by shear stress, would be required. This model for basal release would have to be integrated into the existing model by modifying model parameters so that basal release interacting with myogenic elements would yield a configuration corresponding to an intact AA. Moreover, additional model development would be required to enable independent tracking of both basal and incremental NO release and distribution and to distinguish their respective effects.
Why Model NO Advection Is Significant and NO Scavenging Is Not

Our simulations predict that NO advection can influence downstream vascular tone and that this influence is relatively insensitive to the rate of NO-Hb binding in the lumen, at least in the neighborhood of our base-case parameter values. This prediction arises from the hemodynamic state of a typical renal AA and the relationship between advective transport and NO scavenging.

A comparison of the NO binding rate coefficient with blood transit time through the arteriole helps to explain why NO scavenging may have a minimal impact. AA length is variable, with most AA lengths ranging from ~100 to 400 μm; the mean value in rats, including nonjuxtamedullary AA, is ~140 μm (6). AA luminal diameter is 10–20 μm (8), and single nephron AA blood flow is 200–400 nl/min (33, 34). With these values, the characteristic transit time is on the order of 5 ms (based on length, 140 μm; diameter, 15 μm; flow, 300 nl/min), with a likely range of 3–30 ms. Thus the average transit time is 25% of the half-life of luminal NO with our base-case removal coefficient, which is 20 ms. Hence, although the NO half-life is short, the lifetime of NO is long compared with transit time through an AA. In other vascular beds, with substantially lower flow velocities or longer lengths, the contribution of advective NO transport may be of lesser importance.

NO Scavenging, Release, and VSM Response

The accuracy of the foregoing analysis depends critically on our base-case rate of NO-Hb binding: the results in Fig. 12 show that a 10- or 100-fold increase in binding rate can significantly diminish axial advection of free NO. There is sufficient Hb in blood (2.3 mM), and the coefficient of NO binding by Hb is sufficiently large, to result in a half-life of ~2 μs, if NO had free access to Hb (39). In that case, NO would be an ineffective paracrine agent, because little NO would reach VSM. However, NO does reach VSM, and a number of investigators have sought to determine why NO is not rapidly scavenged by Hb. Three important factors have been identified by means of physiological experiments and mathematical models of radial NO diffusion. First, the RBC-free boundary layer at the vessel wall appears to present a significant barrier to NO diffusion into the lumen (21); our simulations verify this behavior when the fluid is loaded with NO released from upstream. Second, the boundary layer of relatively unstirred fluid surrounding each RBC can impede NO diffusion (23). Finally, Vaughn et al. (38) have recently shown that RBC have an intrinsic barrier to NO that greatly impedes NO-Hb binding; although the mechanisms are unclear, the experimental data suggest that the rate coefficient for free NO binding to Hb within RBC is some 2,000-fold lower than for free Hb. Thus our base-case rate coefficient for NO-Hb binding is likely superphysiological. On the other hand, we have not represented a second mode of NO scavenging, the formation of SNO adducts. However, this process is slower than Hb binding and, like Hb binding, involves some NO entry into RBC (15, 32). Hence, in the kidney, most SNO generation from NO released in the AA likely occurs in downstream segments.

In addition to the questions surrounding NO scavenging in the lumen, nearly every parameter concerning NO has uncertainty associated with it. For example, the rate of NO release can vary widely because it is subject to short- and long-term regulation (42). Furthermore, expression of iNOS by EC can substantially enhance the local release of NO (27). Similarly, the sensitivity of tissues to NO is uncertain. Responses to NO obtained from in vitro studies are typically expressed in terms of bath concentrations rather than local concentrations within tissue. In vivo, uncertainty arises because measurements of NO concentrations in blood or tissue, either in samples or in situ, may represent averages that differ substantially from local concentrations near NO sources or sinks. Thus NO dose-response curves are somewhat variable in relation to the range of relevant concentrations. In our model, we have used incremental release rates and dose-response curves that result in local concentrations of 1–100 nM and responses within this range (24). Other data suggest that the biologically relevant concentration range is an order of magnitude higher (12). However, because the NO concentrations scale linearly with the release rate magnitude, our results do not depend critically on our choice of NO release rate and VSM sensitivity; if the NO dose-response curve is adjusted accordingly, the patterns of NO distribution and transport will remain unchanged.

Physiological Implications

Our simulation studies provide insight into the physiology of NO within the renal microvasculature. Because the transit time of blood through an AA is much less than the half-life of NO, Hb binding and peroxinitrite formation will occur downstream in the glomerular and peritubular capillaries where fluid velocities are lower and transit times longer. Furthermore, the NO concentration of the glomerular filtrate is likely to be similar to that of blood leaving the AA. Because NO is known to influence a variety of transport processes (43), advective NO transport may link arteriolar hemodynamics and proximal tubular transport. In addition, efferent arteriolar tone may be influenced by NO loaded into blood passing through the AA.

The renal vasculature is more sensitive to NO than other vascular beds (43), and our simulations suggest that tissue and blood concentrations of NO will be highest at the end of the AA. This assertion is based on the results shown in Fig. 13, in which the fate of incremental NO release distributed along the vessel can be assumed to approximate the fate of NO basal release. In the boundary layer, NO concentration increased along the vessel owing to both diffusion from the wall and advection from upstream. At the distal end of the vessel, NO diffusion into the abluminal...
region was enhanced because of the high NO concentration in the boundary layer. The distal AA is a site of important processes that are highly sensitive to NO, including renin secretion and TGF (13, 36). Because NO is also produced in macula densa and thick ascending limb cells (31, 44), the convergence of NO-rich fluids at the juxtaglomerular apparatus will likely result in high local concentrations and may have a significant impact on both short- and long-term renal hemodynamic regulation.

Our conclusion that advective transport of free NO may have substantial effects on local NO diffusion as well as on the distribution of NO along the renal microcirculation extends the traditional concept that NO is an important paracrine factor that regulates VSM function. Although we have focused on advective and diffusive transport in a model of a single arteriole, some evidence suggests NO transport over much longer distances. Kon et al. (18) showed that the loss of EC in the main renal artery is sufficient to alter glomerular hemodynamics, suggesting that NO produced in conduit arteries may influence renal function. Furthermore, recent studies by Stamler and colleagues (25, 28) have provided increasing evidence for systemic circulation of NO in RBC, either bound to Hb or as SNO adducts. Of particular relevance to the renal circulation is that in regions with low Po2 (e.g., the renal cortex), free NO may be released from RBC in amounts sufficient to cause vasodilation. If so, this effect would provide a mechanism to explain hypoxic vasodilation, but it would also require that RBC be considered a potential source of NO, rather than only a sink, and an assumption common to many models of NO transport would merit reexamination. Moreover, any release of NO from RBC would add to the importance of advective NO transport.

This study also illustrates how the combination of myogenic reactivity and locally produced NO could act in concert to stabilize arteriolar flow and outflow pressure in response to a focal vasoconstriction in the proximal AA. Enhanced NO release is expected near the vasoconstriction, because of the resulting increase in shear stress along EC; moreover, if the constriction is associated with vascular injury and iNOS expression, local NO release may be further enhanced. Although the contribution of the myogenic mechanism to compensatory downstream vasodilation is predictable from its known characteristics, the results of this study suggest that locally produced NO may be advected in amounts sufficient to augment downstream vasodilation and thereby reinforce myogenic relaxation and more effectively stabilize arteriolar flow.

This research was supported in part by National Institutes of Health Grant DK-42091 (to H. E. Layton) and by the National Science Foundation through Group Infrastructure Grant DMS-9709608 (to M. C. Reed, H. E. Layton, and J. J. Blum). Supercomputer time was supplied by the North Carolina Supercomputing Center in the form of several grants to H. E. Layton.

Present address of K. M. Smith: School of Computational Science and Information Technology, Florida State Univ., Tallahassee, FL 32306-4120.

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