Venular endothelium-derived NO can affect paired arteriole: a computational model

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Kavdia, Mahendra, and Aleksander S. Popel. Venular endothelium-derived NO can affect paired arteriole: a computational model. Am J Physiol Heart Circ Physiol 290: H716–H723, 2006. First published September 9, 2005; doi:10.1152/ajpheart.00776.2005.—Venular endothelial cells release nitric oxide (NO) in response to intraluminal flow both in isolated venules and in vivo. Experimental studies suggest that venular endothelium-derived NO causes dilation of the adjacent paired arteriole. In the vascular wall, NO stimulates its target hemoprotein, soluble guanylate cyclase (sGC), which relaxes smooth muscle cells. In this study, a computational model of NO transport for an arteriole and venule pair was developed to determine the importance of the venular endothelium-derived NO and its transport to the adjacent arteriole in the tissue. The model predicts that the tissue NO levels are affected within a wide range of parameters, including NO-red blood cell reaction rate and NO production rate in the arteriole and venule. The results predict that changes in the venular NO production affected not only venular endothelial and smooth muscle NO concentration but also endothelial and smooth muscle NO concentration in the adjacent arteriole. This suggests that the anatomy of microvascular tissue can permit the transport of NO from arteriole to venule side, and vice versa, and may provide a mechanism for dilation of proximal arterioles by venules. These results will have significant implications for our understanding of tissue NO levels in both physiological and pathophysiological conditions.

VASCULAR ENDOTHELIAL CELLS release nitric oxide (NO) through enzymatic conversion of L-arginine by endothelial NO synthase (eNOS). The major target of NO is in the smooth muscle cells, where it activates the enzyme soluble guanylate cyclase (sGC), which catalyzes the conversion of GTP to cGMP and causes vasodilation (19).

Endothelial cells line both arteriolar and venular vessels. The rate at which endothelial cells release NO increases upon exposure to the shear stress caused by flowing blood or to other agonists. Many studies have shown close pairings of larger arterioles and venules in the microcirculation, and a few studies have demonstrated physiological significance of such an arrangement (12, 16, 31, 48). Some of these studies have demonstrated that substances including soluble gases can be transported between paired arteriole and venule. This transport of vasoactive mediators from venule could control arteriolar tone. The hypothesized mediators involved in venular control of arteriolar tone include prostaglandins, arachidonic acid, and NO (12, 16, 17).

A number of studies have examined the role of venular control of arteriolar tone in a closely paired arrangement. Using segments of first-order arterioles and venules isolated from skeletal muscle and connected in series, Falcone and Meininger (12) reported that the venular endothelium-derived NO can cause arteriolar dilation. Diffusion of vasoactive substances from a venule to a paired arteriole was reported in several studies by Hester and colleagues (16, 17). Boegehold (1) reported that a shear-dependent release of NO by venular endothelium affected paired arteriole dilation. Nellore and Harris (34) reported that venule-released NO contributed to arteriolar NO. This venular contribution to arteriolar NO was significantly reduced in diabetic rats.

Experimental studies (3, 5, 21, 41) have been performed to quantify the physiological and pathophysiological levels of NO in different microcirculatory preparations. Bohlen and colleagues (2–7) used NO microelectrodes developed by Buerk et al. (8) to measure NO concentrations in various regions of rat intestinal microvasculature. In these studies, arterial wall NO concentrations ranged between 340 and 400 nM, and parenchymal cell NO concentrations ranged between 70 and 140 nM. Tsai et al. (41) reported that the periarteriolar and perivenular NO concentrations in a high-viscosity plasma-perfused hamster subjected to extreme hemodilution were the same, although arteriolar shear stress was significantly greater than venular shear stress. Using the NO-sensitive dye diaminofluorescein-2, Kashiwagi et al. (21) reported that NO bioavailability in venules was supported through venular eNOS in an autocrine manner.

The role of microvascular architecture in NO transport has not been as thoroughly investigated as that in oxygen transport. Pittman (35) reviewed both experimental and theoretical studies on the contributions of the arterioles, capillaries, and venules and microvascular hemodynamics to oxygen transport. The review reported that the proximity of capillaries, arterioles, and venules provides the complex spatial relationships that lead to diffusive interactions between capillaries and nearby arterioles and venules, and between paired arterioles and venules. A mathematical model for oxygen transport in a paired arteriole and venule was developed by Sharan and Popel (38) to predict longitudinal gradients of hemoglobin (Hb)-oxygen saturation along the arteriole and venule; the effect of this countercurrent transport was shown to be small, except in the case of low flow conditions.

A model of NO transport for a paired arteriole and venule is not available. Combining reaction kinetics and diffusion, the-
oretical models of NO transport in the microcirculation primarily have considered a single arteriolar vessel (9, 23, 27, 44, 45). These models have provided useful predictions including (1) the factors affecting NO levels in vessel wall (9, 42, 45), (2) the role of myoglobin (22, 24), (3) the contribution of different isoforms of NOS (22, 26), and (4) the interactions of NO and oxygen in the microcirculation (25, 26).

In this study, we developed a paired arteriole-venule NO transport model. The model is used to provide quantitative knowledge regarding NO transport from venular endothelium to adjacent arteriole.

**MATHEMATICAL MODEL**

**Model geometry.** We have modeled a tissue containing a paired arteriole and venule (Fig. 1). Arteriolar and venular blood vessels are divided into the following regions of concentric cylinders: luminal red blood cell (RBC)-free (CF) and RBC-rich (CR) regions, endothelium (E), interstitial space (IS) between the endothelial and smooth muscle cells, smooth muscle layer (SM), and a small, nonperfused parenchymal tissue (NPT) region. Beyond the nonperfused parenchymal tissue region is a parenchymal tissue (PT) region perfused by capillaries extending sufficiently far from the paired vessels.

NO is produced at the luminal and abluminal surfaces of endothelium. NO production is incorporated as surface NO release in boundary conditions at the endothelial interfaces. In the cell-rich luminal region, a homogeneous solution of RBCs is considered. For the perfused parenchymal tissue region, the capillaries and the parenchymal cells are modeled as a distributed homogeneous medium (24), described in detail below.

Previously, we have shown that (1) the convective transport of NO can be neglected because of its fast reaction with Hb (23) and 2) the NO profiles reach steady state within milliseconds (42). Thus it is suitable to solve for the NO mass transport in the vessels and surrounding tissue by using the steady-state NO mass transport equation, written as

\[ D_{NO} \nabla^2 C_{NO,i} + \sum R_i = 0 \]  

where \( C_{NO,i} \) is the NO concentration and \( D_{NO} \) is the NO diffusivity. The net NO reaction rate, \( R_i \), is the sum of individual NO reaction rates and NO production in region \( i \) as described below.

**Boundary conditions.** At the interfaces, boundary conditions of continuity of NO flux and concentration are imposed, except for interfaces at 1) the outer edge of the capillary-perfused parenchymal region, where a zero-flux boundary condition is applied, and 2) the luminal CF region-endothelium interface (Eq. 2a) and the endothelium-interstitial space (Eq. 2b) interface, where boundary conditions incorporate NO release from the endothelium

\[ Q_{NO} = D_{NO} \frac{\partial C_{NO,CF}}{\partial r} - D_{NO} \frac{\partial C_{NO,E}}{\partial r} \]  

where \( Q_{NO} \) is one-half of the total endothelial NO release. Equations 2a and 2b apply to both arteriolar and venular blood vessels. NO release from endothelial cells of arteriole and venule might be different (1); thus \( Q_{NO} \) may have different values for these vessels and is discussed in **Model parameters**.

**Chemical reactions.** The model geometry contains six separate regions i: CR, CF, E, IS, SM, and NPT around each arteriole or venule; and one common PT region. For the luminal RBC-rich region, NO is assumed to react with Hb contained inside RBCs

\[ R_{NO,CR} = k_{CR} C_{NO} \]  

where \( k_{CR} \) is the effective NO reaction rate constant and is a function of the NO reaction rate with RBC Hb, Hb concentration in a single RBC, and core hematocrit (Hct). In the luminal CF region, NO reacts with constituents in the plasma such as thiols, vitamins, plasma-based free Hb, and superoxide (O_2^-). We assume zero Hct in this region. This region also could include an endothelial glyocalyx. We assume a pseudo-first-order reaction with a rate constant \( k_{CF} \) in the luminal CF region

\[ R_{NO,CF} = k_{CF} C_{NO} \]  

We assume that NO reacts with \( O_2 \) in the E, IS, and NPT regions. \( R_{NO} \) for these regions is expressed as

\[ R_{NO,i} = k_{O_2} C_{NO,i} C_{O_2} \]  

where \( i \) stands for E, IS, or NPT; \( k_{O_2} \) is the NO reaction rate with \( O_2 \); and \( C_{O_2} \) is the \( O_2 \) concentration in the region. The reaction between NO and \( O_2 \) is the second order in \( NO \) (28).

In the SM region, NO is consumed by vascular smooth muscle sGC (46) in a second-order reaction with a rate constant \( k_{SM} \)

\[ R_{NO} = k_{SM} C_{NO}^2 \]  

For the capillary-perfused PT region, we assume that NO is consumed by blood flowing in capillaries and NO is produced by capillary endothelial cells. For this region, \( R_{NO} \) is expressed as
\[ R_{NO} = k_{cap} C_{NO} - Q_{cap} \]  

where \( k_{cap} \) is the effective NO reaction rate constant for blood flowing in capillaries in parenchymal tissue and is a function of capillary hematocrit (Hct) and fractional capillary volume. Capillary endothelial cell-released NO (Q_{cap}) in the PT region is distributed uniformly over the tissue volume. Q_{cap} is a function of capillary radius, capillary endothelial NO release rate, and fractional capillary volume.

Parameter values. Model parameter values used for the simulations are presented in Table 1. Based on reported observations of an \( \sim 0.4 – 0.5 \) ratio of paired arteriole-to-venule radius (1, 34), an arteriole-to-venule radius ratio of 0.5 is assumed. Rationales for other geometrical parameters (e.g., wall thickness and radius) are described in detail in earlier publications (22, 24).

Based on experimental measurements by Malinski et al. (30), an NO diffusivity of \( 3.3 \times 10^{-5} \text{ cm}^2/\text{s} \) is assumed, and it is assumed to be the same in all regions. The value of \( k_{CR} \) is 1,270 \text{ s}^{-1}, obtained by multiplying the reported rate of reaction of 1.4 \times 10^8 \text{ M}^{-1} \text{s}^{-1} \text{ of NO with RBC Hb (10), a heme concentration of 20.3 mM in a single RBC, and a core Hct of 0.45. The value of \( k_{O_2} \) is 9.6 \times 10^9 \text{ M}^{-2} \text{s}^{-1} \text (28), and in vivo C_{O_2} is \( \sim 27 \mu\text{M}, corresponding to a partial pressure of 15.5 \text{ mmHg (36). However, because of the slow reaction of NO and O2, the NO profiles presented in this model were not affected even for significant changes in C_{O_2} that are present in various regions of tissue. The value of \( k_{SM} \) estimated for vascular smooth muscle sGC is \( 5 \times 10^4 \text{ M}^{-1} \text{s}^{-1} \text (46). The value of \( k_{cap} \) is 12.4 s^{-1}, calculated from a Hct of 0.3 and a fractional capillary volume of 0.0146 [a capillary density of 1,435 mm^{-2} and a capillary radius of 1.8 \mu\text{m}, based on hamster retractor muscle (11)].

The production rate of NO in this study is limited to the arteriolar, venular, and capillary wall. We use a NO production control value of 2.65 \times 10^{-12} \text{ mol cm}^{-2} \text{s}^{-1} for both the luminal and abluminal sides of the arteriolar and venular wall endothelium based on experimental data by Malinski et al. (30) in rabbit aorta. The same NO production rate per unit surface area for the capillary is assumed. The value of Q_{cap} is estimated to be \( 8.6 \times 10^{-7} \text{ M} \) in tissue containing a paired arteriole and venule. Arteriolar and venular diameter is 50 and 100 \mu\text{m}, respectively, and luminal centers are 100 \mu\text{m} apart. Profile is shown for a luminal red blood cell (RBC)-rich region NO-RBC reaction rate of 1,270 \text{ s}^{-1} and equal production of NO in arteriolar, venular, and capillary endothelium.

Table 1. Model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hematocrit, %</td>
<td>45</td>
<td>Text</td>
</tr>
<tr>
<td>Capillary hematocrit, %</td>
<td>30</td>
<td>Text</td>
</tr>
<tr>
<td>Arteriolar vessel radius, \mu m</td>
<td>25</td>
<td>Text</td>
</tr>
<tr>
<td>Venular vessel radius, \mu m</td>
<td>50</td>
<td>Text</td>
</tr>
<tr>
<td>Distance between centers of arteriole and venule, \mu m</td>
<td>100</td>
<td>Text</td>
</tr>
<tr>
<td>Arteriolar CF layer thickness, \mu m</td>
<td>4.5</td>
<td>(39)</td>
</tr>
<tr>
<td>Venular CF layer thickness, \mu m</td>
<td>2.0</td>
<td>(39)</td>
</tr>
<tr>
<td>E thickness, \mu m</td>
<td>0.5</td>
<td>(47)</td>
</tr>
<tr>
<td>IS thickness, \mu m</td>
<td>0.5</td>
<td>(24)</td>
</tr>
<tr>
<td>SM thickness, \mu m</td>
<td>6</td>
<td>(15)</td>
</tr>
<tr>
<td>NPT thickness, \mu m</td>
<td>5</td>
<td>Text</td>
</tr>
<tr>
<td>( O_2 ) concentration, \mu M</td>
<td>27</td>
<td>(36)</td>
</tr>
<tr>
<td>NO release rate (2 \times Q_{NO}), \text{mol cm}^{-2} \text{s}^{-1}</td>
<td>5.3 \times 10^{-12}</td>
<td>(46)</td>
</tr>
<tr>
<td>( D_{NO} ), \text{cm}^2/\text{s}</td>
<td>3.3 \times 10^{-5}</td>
<td>(30)</td>
</tr>
<tr>
<td>Reaction rates of NO with ( O_2 ): ( k_{O_2} ) \ M^{-2} \text{s}^{-1}</td>
<td>9.6 \times 10^6</td>
<td>(28)</td>
</tr>
<tr>
<td>( sGC ): ( k_{sGC} ) \ M^{-1} \text{s}^{-1}</td>
<td>5 \times 10^4</td>
<td>(46)</td>
</tr>
<tr>
<td>( RBC )-rich: ( k_{RBC} ) \ M^{-1} \text{s}^{-1}</td>
<td>1.4 \times 10^8</td>
<td>(10)</td>
</tr>
<tr>
<td>( CR )-rich: ( k_{CR} ) \ s^{-1}</td>
<td>1.270 (635–5,080)</td>
<td>Text</td>
</tr>
<tr>
<td>Capillaries: ( k_{cap} ) \ s^{-1}</td>
<td>0.1</td>
<td>Text</td>
</tr>
</tbody>
</table>

RESULTS

Steady-state NO profiles for a paired arteriole-venule. Figure 2 shows the steady-state NO concentration distribution in a tissue containing a paired arteriole (diameter \( D = 50 \mu\text{m} \)) and venule (\( D = 100 \mu\text{m} \)) with their luminal centers 100 \mu\text{m} apart. For these calculations, a luminal RBC-rich region reaction rate of 1,270 \text{ s}^{-1}, a parenchymal reaction rate of 12.4–8.6 \times 10^{-7} \times C_{NO} \text{s}^{-1}, and the same arteriolar, venular, and capillary endothelial cell NO production values were used. The tissue, endothelium, and smooth muscle NO concentrations vary with location in respect to the arteriolar or venular vessel. The tissue surrounding the arteriole has a higher NO concentration com-
Table 2. NO concentration at selected locations for different parenchymal reaction rates

<table>
<thead>
<tr>
<th>Location</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolar smooth muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On left NPT region side (P1)</td>
<td>93</td>
<td>110</td>
</tr>
<tr>
<td>On right E side (P2)</td>
<td>103</td>
<td>113</td>
</tr>
<tr>
<td>On right NPT region side (P4)</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>Venular smooth muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On left NPT region side (P3)</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>On left E side (P6)</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>On right NPT region side (P8)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Arteriolar endothelium (max concentration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On left</td>
<td>104</td>
<td>114</td>
</tr>
<tr>
<td>On right</td>
<td>103</td>
<td>106</td>
</tr>
<tr>
<td>Venular endothelium (max concentration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On left</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>On right</td>
<td>66</td>
<td>66</td>
</tr>
</tbody>
</table>

Case 1 represents the NO concentrations (CNO) from Fig. 2 for a parenchymal reaction rate resulting from blood flow in the tissue capillaries. Case 2 represents the CNO for a parenchymal reaction rate resulting from NO consumption by oxygen only.

pared with the tissue surrounding the venule. Both the arteriolar and the venular RBC-rich luminal region has NO. The arteriolar endothelium has a higher NO concentration than that of the venule. The arteriolar smooth muscle closer to and farther from the venule has similar NO concentrations. On the contrary, the venular smooth muscle closer to the arteriole has a much higher NO concentration than that farther from the arteriole.

Table 2 shows the NO concentration at several locations in the tissue. In Table 2 and elsewhere in the article, the concentrations are shown along the line passing through the centers of the vessels in the X direction in Fig. 2. The definition of points P1–P8 along this line (see Fig. 3) is given in Table 2. The NO concentration of 97 nM (average of NO concentrations of 102 and 92 nM at P1 and P2, respectively) of the arteriolar smooth muscle closer to the arteriole is higher than the NO concentration of 66 nM (average of NO concentrations at P3 and P4) of the venular smooth muscle farther from the arteriolar vessel. Thus the presence of a nearby arteriole can influence the venular wall NO levels.

**NO reaction with RBCs.** At physiological hematocrit, the reaction rate of a RBC suspension with NO is not known. The reaction of NO with Hb contained inside a RBC is under intense investigation. It is established that the effective reaction rate of NO with Hb contained in a RBC is two to three orders of magnitude lower than the reaction rate with free Hb (18, 29). Using a mathematical model, Tsoukias and Popel (43) predicted that the NO reaction rate with RBC suspension is 750–6,500 s⁻¹ and is a function of hematocrit. We varied the rate of the NO reaction with RBCs from one-half to four times the control value of 1.4 × 10⁵ M⁻¹·s⁻¹ reported for <1% hematocrit (10). This results in a range of kCR between 635 and 5,080 s⁻¹, which is the first-order reaction rate in the RBC-rich luminal region. Figure 3 shows the resulting NO concentration profiles. An eightfold variation in the reaction rate of NO-RBC changes NO concentration from 122 to 79 nM at P2 and from 135 to 73 nM at P3 on the luminal side of the arteriolar smooth muscle. At the luminal side of the venular smooth muscle, NO concentration changes from 87 to 50 nM at P3 and from 81 to 42 nM at P4 for the eightfold change in NO-RBC reaction rate. Thus the eightfold variation in NO-RBC reaction rate changes the smooth muscle NO concentration 1.5- to twofold. In addition, higher values of this reaction rate of 1,270–5,080 s⁻¹ do not have as much of an effect on the NO profiles as the lower values of 635–1,270 s⁻¹.

**Effect of parenchymal reaction rate on NO profile.** For the control value, we used a parenchymal reaction rate corresponding to a homogeneous distribution of capillaries, which may overestimate the NO consumption (44). This results in a term for NO reaction from capillary blood and a term for NO production from capillary endothelium (Eq. 7); NO profiles are shown in Fig. 3. We also simulated NO concentration profiles for a reaction rate resulting from oxygen consumption of NO in the parenchymal tissue region (Fig. 4); the reaction rate is the same as that defined in Eq. 5. These simulations demonstrate that the parenchymal tissue reaction rate does not have a...
significant effect on NO concentration in the smooth muscle (Fig. 4). The second-order NO reaction with oxygen is slow, resulting in an essentially flat concentration profile throughout the parenchymal tissue and yielding an increase in the NO concentration in the arteriolar and the venular smooth muscle.

In Table 2, case 2 represents the NO concentrations for the luminal RBC-rich reaction rate of 1,270 s$^{-1}$ and the parenchymal tissue region reaction rate resulting from NO and oxygen interaction. The NO concentration of the arteriolar smooth muscle is 110, 113, 105, and 95 nM at P1–P4, respectively, and that of the venular smooth muscle is 80, 72, 66, and 66 nM at P5–P8, respectively. Hence, a maximum of 10% change occurs when only oxygen consumption is used as the parenchymal tissue reaction rate. Thus we can expect that the resulting NO concentration predictions in the regions of interest (endothelium and smooth muscle) will be approximately independent of parenchymal tissue reaction rate.

In addition, Fig. 4 shows the NO profiles for this case when the luminal RBC-rich region reaction rate is varied. The luminal RBC-rich region reaction rate of 635–5,080 s$^{-1}$ changes NO concentration from 127 to 97 nM (or 24%) at P2 and from 118 to 89 nM (or 25%) at P3 on the luminal side of the arteriolar smooth muscle. On the luminal side of the venular smooth muscle, NO concentration changes from 85 to 56 nM (or 34%) at P6 and from 77 to 51 nM (or 34%) at P7. When we compare the respective profiles from Figs. 3 and 4 and NO concentration at P2, P3, P6, and P7, a much smaller reaction rate of NO consumption by oxygen in the parenchymal region does not significantly change NO concentration in either the smooth muscle or the endothelium.

Venular NO production. Figure 5A shows the tissue NO levels for a 0.5 reduction in the venular endothelial NO production rate with all other parameters kept constant. The decrease in the venular NO production reduced the NO concentration in the surrounding area of the venule (for comparison, see Fig. 2). Figure 6 shows the NO concentration profiles for 0.1 to 3 times the control venular NO production. An increase in NO production increases, and a decrease in NO production decreases, NO concentration around the venule. Note that changes in the venular NO production changed not only the venular endothelial and smooth muscle concentrations but also the arteriolar endothelial and smooth muscle NO concentrations. For two- and threefold increases in the venular...
endothelium NO production, there is net diffusion of NO toward the arteriolar smooth muscle. These results demonstrate that the NO released from the venular endothelium has potential to affect a nearby arteriole.

**Arteriolar NO production.** Figure 5B shows the tissue NO levels for a 0.5 reduction in the arteriolar endothelial NO production rate. The reduced arteriolar endothelial NO production has significantly reduced NO concentration in the surrounding regions of the arteriole (for comparison, see Fig. 2). In addition, the same percent change in the endothelial NO production of arteriole compared with venule has a much higher reduction in the NO concentration (Fig. 5, A vs. B). Figure 7 shows the concentration profiles for varying arteriolar endothelial NO production. An increase in NO production increases, and a decrease in NO production decreases, NO concentration around the arteriole. Note that the venular smooth muscle has a higher NO concentration than the arteriolar smooth muscle for 0.25 and 0.5 the control arteriolar endothelial NO production. Therefore, the venule-derived NO diffuses to the adjacent arteriole and can significantly affect the NO concentration in its vascular wall.

**DISCUSSION**

**Implications for in situ measurements of NO.** Results from the present and earlier models have established that the NO concentration gradients are steep in the vascular wall. Micro-electrodes and fluorescent dyes have been used to measure the NO levels in various regions of microvessels in several vascular beds (21, 41). Even though great advances have been made in NO measurements, the spatial resolution of the methods has not been sufficient to measure these steep NO gradients.

Although in the present model we have only considered NO released from the arteriolar and venular endothelium, other possible NO sources that can contribute to microvascular NO levels include mitochondrial NOS, inducible NOS, and neuronal NOS; however, the contribution of mitochondrial NOS to tissue NO is controversial (13). Kavdia and Popel (22) and Lamkin-Kennard et al. (26) predicted that the neuronal NOS can contribute significantly to the tissue NO levels. The release of NO from all these NOS isoforms is dependent on the oxygen concentration. However, the oxygen dependency of NO production from endothelial NOS should not be significantly affected, because the half-maximal concentration of oxygen-dependent NO production is 4.7 Torr (37), compared with an assumed average tissue oxygen concentration of 15.5 Torr in these simulations. Tissue PO2 varies between 0 and ~30 Torr in vivo; therefore, the results may be different in hypoxic tissue. The NO concentrations may exhibit wide regional heterogeneity, reflecting variations in the distribution and expression levels of NOS in vascular beds, and further experi-
mental and theoretical investigations are required to determine availability of NO in specific tissues.  

Physiological role of arteriolar-venular NO transport. Many studies have shown a functional role for the arteriolar endothelium in the regulation of vascular tone and blood flow. In recent years, several research groups have studied experimentally the effect of venular endothelium on the regulation of arteriolar diameter (1, 12, 16, 17, 33, 34). Some of these studies have focused on the diffusion of NO from venule to arteriole. The model results presented in this article suggest that the diffusion of NO from venule to arteriole is possible and significant under certain conditions (e.g., NO profiles for 2 and 3 times control venular endothelial NO production in Fig. 6 and 0.25 and 0.5 times control arteriolar endothelial NO production in Fig. 7). When venular NO release rates are changed, the peak concentrations in the arteriolar endothelium and the smooth muscle are changed, as shown in Fig. 6. This suggests that the venular endothelium affects NO levels in the arteriolar endothelium. These model predictions are supported by 1) correlation between shear stress-dependent changes in venular NO release and the magnitude of arteriolar dilation reported by Boegehold (1), and 2) venular eNOS as a major source of NO availability in the rat mesentery compared with arteriolar eNOS observed by Kashiwagi et al. (21).

Studies have reported distinct differences in endothelial NO release and its effect within a specific vascular bed (40). Some trends are emerging from experimental and theoretical research, including NO levels in the tissue and in the vascular wall in the range of several tens to a few hundred nanomolar, depending on type of vasculature and specific location in the tissue. Figures 2 and 3 show that even for equal NO release rates, the concentration of NO in the arteriolar wall is higher than that in the venular wall, because of a smaller venular luminal RBC-free region of 2.0 μm compared with an arteriolar luminal RBC-free region of 4.5 μm. When we increase the venular luminal RBC-free region thickness from 2.0 to 4.5 μm, NO concentration at points P1−P8 changes to 83, 103, 110, 106, 104, 106, 99, and 91, respectively (Table 2 contains concentrations for 4.5 μm). For both vessels, the peak NO concentrations are at the endothelium. In most cases, the venular endothelium nearest the center of the arteriole has a higher peak value than that farther away from the arteriolar center, whereas the arteriolar endothelium farthest away from the venular center has a higher peak NO concentration.

The model predictions of ~30% lower NO concentration in the venular endothelium compared with the arteriolar endothelium are also similar to the reported ~25% lower NO concentration in paired venules and arterioles by Nase et al. (32). Although the magnitude of the difference is similar, the NO concentration predicted in the present model is significantly different from the measured one. The predicted NO concentrations are in the range of 104 and 69 nM for the arteriolar and the venular endothelium, respectively (Table 2, case 1), compared with a measured NO concentration of 397 and 298 nM, respectively (32). This high NO concentration can be obtained from the present model by 1) increasing endothelial NO release (see Fig. 7), given that estimates of NO release rate for microvascular endothelial cells are not available; 2) reducing the NO reaction rate with RBCs (see Fig. 3), because this reaction rate is not available at physiological hematocrit (43); and 3) incorporating other sources of NO production in the tissue (22). However, we point out that the NO concentration predictions from this model are consistent with other NO transport models (9, 23–26, 42, 45).

Pathological conditions: effect on arteriolar-venular NO. NO-mediated vasodilation is attenuated in diabetes, aging, and hypercholesterolemia conditions. The transport of NO from arteriole and venule may be affected. One of the important results of our study is that the arteriolar-derived NO can reach the venular side, and vice versa. In the case of diabetes, leukocyte adhesion at the venular side of the microcirculation is known to increase. Because of increased tissue oxidative stress from hyperglycemia, it may be possible that NO is scavenged by reactive oxygen species, and NO production is decreased. The adherent leukocytes on the venular side can become a site of inflammation and increase tissue oxidative stress through release of reactive oxygen species, reducing NO bioavailability and causing arterioles to constrict further. Nellore and Harris (34) reported an increase in arteriolar NO by venular shear in normal rats but not in diabetic rats.

Another condition in which venular NO transport may play a role is in ischemia-reperfusion injury. To demonstrate the importance of the role of NO in decreasing the neutrophil-endothelial interactions associated with ischemia-reperfusion injury, Gabriel et al. (14) reported that the administration of L-arginine significantly reduced leukocyte adhesion to venular endothelium during reperfusion compared with the ischemia-reperfusion group. Furthermore, the administration of nitro-L-arginine methyl ester with L-arginine showed no significant difference in adherent leukocytes compared with the ischemia-reperfusion group. Based on the model predictions, the findings of Gabriel et al. (14) can be interpreted as follows: 1) L-arginine administration could increase NO production in arteriolar and/or venular endothelium and subsequently increase levels of NO in the venular endothelium, and 2) nitro-L-arginine methyl ester administration could decrease NO production in arteriolar and/or venular endothelium and subsequently decrease levels of NO in the venular endothelium.

In conclusion, we have presented for the first time a computational model of NO transport for a paired arteriole and venule. The model results suggest that the transport of NO from the arteriole to the venule, and vice versa, is possible and that its impact can be significant. These results will have significant implications for our understanding of changes in tissue NO levels in both physiological and pathophysiological conditions.

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