Opposing effects of L-NAME on capillary filtration rate in the presence or absence of neutrophils

NORMAN R. HARRIS
Department of Molecular and Cellular Physiology,
Louisiana State University Medical Center, Shreveport, Louisiana 71130-3932

Harris, Norman R. Opposing effects of L-NAME on capillary filtration rate in the presence or absence of neutrophils. Am. J. Physiol. 273 (Gastrointest. Liver Physiol. 36): G1320-G1325, 1997.—Fluid filtration rate (Jv/S) from rat mesenteric capillaries was measured using a modified Landis technique before and after superfusion with 100 µM N(G)-nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor. Three groups were studied: 1) control rats, 2) rats injected with antineutrophil serum (ANS), and 3) rats injected with a monoclonal antibody (CL26) against the leukocyte adhesion molecule CD18. The relative increase in Jv/S (L-NAME/baseline) in control rats averaged 1.66 ± 0.32 (n = 11), which was significantly higher (P < 0.05) than in ANS (0.51 ± 0.12; n = 5)- and CL26 (0.45 ± 0.16; n = 6)-injected rats exposed to L-NAME. The L-NAME-induced changes in Jv/S in each group were due to altered permeability rather than altered pressure gradients, as determined by measurements of arteriolar hydrostatic pressure (using a servo-null apparatus) and estimates of intravascular oncotic pressure (using plasma protein concentration). These findings indicate that nitric oxide synthase inhibition increases the permeability of mesenteric capillaries to water, a response that is dependent on neutrophil adhesion.

NITRIC OXIDE (NO) is known to play an important role in many physiological processes, including endothelium-dependent vascular relaxation. An existing controversy in microcirculation research relates to the effect of NO on microvascular permeability, with some reports promoting a protective role (3, 17, 23) and others promoting the opposite (21, 22). One condition in which NO-mediated microvascular permeability is of prime concern is ischemia-reperfusion (I/R), during which the bioavailability of NO decreases (5), possibly due to a reaction with superoxide. The decrease in NO is thought to be detrimental inasmuch as administration of NO donors or L-arginine (a precursor of NO) attenuates reperfusion-induced postcapillary leukocyte adhesion and protein leakage (17, 23). Additional support of a protective role for NO comes from studies (15, 16, 18) of the effect of NO synthase inhibitors, such as N(G)-nitro-L-arginine methyl ester (L-NAME), which, similar to I/R, elicits protein leakage and leukocyte adhesion in postcapillary venules of the rat mesentery. The increase in postcapillary protein leakage during I/R and during L-NAME superfusion appears to be directly related to the level of leukocyte adhesion (14, 15). This relationship appears to be confirmed by an attenuation of protein leakage with interventions that inhibit leukocyte adhesion.

Much of the information concerning the role of NO in acute inflammation has come from observations of postcapillary venules, and little information is available on the role of NO on capillary exchange. However, a study by Rumbaut et al. (24) in the frog mesentery demonstrated that NO synthase inhibition with N(G)-monomethyl-L-arginine (L-NMMA) decreases capillary hydraulic conductivity, with the effect reversed (not just attenuated) in the presence of excess L-arginine. Even though this observation appears to contradict the results obtained in rat mesenteric venules, in which L-NAME increases protein permeability (15, 16, 18), the experiments in the frog were performed by cannulating the capillaries and perfusing the vessels with a solution of buffer and human red blood cells, but no leukocytes. Considering the known influence of leukocyte adhesion on vascular permeability, it is possible that the experiments in the frog mesentery represent the direct effect of NO (and its inhibition) on endothelial cells, an effect that may differ in the presence of leukocytes.

The increased postcapillary permeability associated with acute inflammation is accompanied by adhesive interactions between leukocytes and endothelial cells that include rolling, firm adherence, and emigration. Leukocyte adhesion is mediated by the CD11/CD18 heterodimer, which is located on the leukocyte surface. Inhibition of leukocyte adhesion with a monoclonal antibody (CL26) directed against the CD18 subunit has been successful in attenuating increases in postcapillary permeability during L-NAME superfusion of mesentery (15) and during I/R (14). Upstream from the postcapillary venules, the same monoclonal antibody as well as antineutrophil serum (ANS) have each been shown to attenuate the increase in capillary permeability, as determined by increased fluid filtration rate (Jv/S), after exposure to platelet-activating factor (PAF) (8). It remains to be determined whether CL26 and ANS also influence the response of capillaries in other models of acute inflammation.

Therefore, the specific objectives of this study were to determine the effect of NO synthase inhibition on the permeability of individual capillaries in the rat, and also to determine the role that neutrophils and neutrophil adhesion play in this process. To accomplish these objectives, Jv/S was measured in capillaries of rat mesentery before and after superfusion with L-NAME. Three groups underwent L-NAME superfusion: 1) control rats, 2) rats treated with ANS, and 3) rats treated with CL26.

METHODS

Animal preparation. Forty-six male Sprague-Dawley rats were fasted overnight, then anesthetized with an intraperito-
neal injection of 130 mg/kg thiobutabarbital (Inactin). A thoracotomy was performed to facilitate breathing, the right carotid artery was cannulated to monitor systemic blood pressure, and the left jugular vein was cannulated for administration of an overdose of pentobarbital sodium (160 mg/kg) at the conclusion of each experiment. The small intestine was exteriorized through a midline abdominal incision, and the rat was placed on its side on a Plexiglas board so that a selected section of mesentery could be draped over a glass coverslip glued on a hole centered in the board. The exposed intestine, except for the selected mesenteric section under study, was covered with gauze soaked in bicarbonate-buffered saline (BBS) consisting of 132 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 20 mM NaHCO3, and 2.0 mM CaCl2. After the board was mounted onto the stage of an inverted microscope (Nikon Diaphot), the mesentery and intestine were kept moist by a 2 ml/min superfusion of BBS bubbled with a 95% N2-5% CO2 gas mixture and warmed to 37°C. Rectal temperature was monitored and maintained near 37°C by positioning an infrared heat lamp over the rat.

Video microscopy. The mesentery was observed through a ×40 objective (0.85 NA, Nikon Fluor 40) using a 100 W halogen light source, and bright-field images were captured with a color camera (Hitachi VK-C150). The images were then directed through a time-date generator (Panasonic WJ-810) into a video cassette recorder (JVC BR-S601MU), with the live image displayed on a monitor (Sony Trinitron) and the taped image used for playback analysis using an image grabber (Imaging Technology Visionplus, Bedford, MA) and image processor (BioScan Optimas, Edmonds, WA).

Measurement of capillary filtration. Capillary Jv/S was measured using a modified Landis technique (19). As described previously (8, 9, 10), a selected capillary was occluded and Jv/S was determined from the decreasing distance between two red blood cells (20). All selected capillaries had diameters <10 µm and were “true” capillaries, i.e., divergent at the upstream end and convergent at the downstream end. Each selected capillary was briefly occluded near its venous end with a micropipette drawn to a tip diameter of ~5 µm. The micropipette tip was rounded with a microforge (Stoelting, Wood Dale, IL) to minimize damage to the capillary during placement on its side on the microscope stage. The micropipette was accomplished with the use of a micromanipulator (Narishige MO-302) mounted on the microscope. During capillary occlusion, individual red blood cells within the vessel gradually moved closer together and toward the occlusion site as intravascular fluid separating the cells filtered across the endothelial barrier into the surrounding tissue. To measure Jv/S, two red blood cells ~100 µm apart were selected, and the distance between those cells was monitored for a period of 16 s.

After an occlusion, the decreasing distance between the two cells (x) was used to calculate Jv/S by dividing the volume filtered (Jv) by a given time period and normalizing to the surface area (S) of the capillary segment containing the two cells. (The capillary geometry was assumed to be a uniform circular cylinder.) The calculation of Jv/S can be simplified and expressed as

\[
\frac{J_v}{S} = \frac{-D}{4x} \frac{dx}{dt}
\]

in which D is diameter. The change in x with respect to time (dx/dt) was measured with an image processor during playback of the videotape in seven 2-s periods beginning 2 s after the occlusion, and the average Jv/S of the seven periods was computed. The measurement was not made during the first 2 s of the occlusion, because there may be a brief vascular expansion during this period due to a higher intravascular pressure (1, 26); capillary pressure will increase to equal arterial pressure after an occlusion. The seven 2-s measurements required that the capillary be occluded for a total of 16 s, which was long enough to obtain an accurate estimate of Jv/S but brief enough to allow consistent capillary reflow when the pipette was lifted. In each measurement, the downstream red blood cell was chosen so that it was at least 25–35 µm from the occlusion site where the pipette flattens the shape of the capillary and impedes cell movement. The second cell was chosen as far upstream on the video monitor as possible, typically including 100 µm of capillary length. Each capillary under study was occluded once during baseline conditions and once after L-NAME superfusion. Because the pipette may damage the capillary at the occlusion site, the second occlusion was made ~5–10 µm upstream of the first site, so that any damage incurred by the first occlusion would not affect the filtration measurement of the second occlusion. When more than one capillary per rat was used to estimate Jv/S, the values of Jv/S were pooled to generate an average value per rat.

Although altered Jv/S can reflect a change in permeability, it can also reflect changes in hydrostatic or osmotic pressure. Starling’s equation describes the factors that determine the rate at which the fluid filters

\[
\frac{J_v}{S} = \frac{L_p}{S} (P_c - P_l - \sigma (P_i - P_r))
\]

where Lp is hydraulic conductivity, Pc is capillary hydrostatic pressure, Pl is interstitial hydrostatic pressure, σ is the osmotic reflection coefficient, Pir is capillary osmotic pressure, and Pri is interstitial osmotic pressure. Because the mesentery was exteriorized and superfused with protein-free buffer, both Pir and Pri should be ~0 mmHg. Additionally, the hydrostatic pressure in the occluded capillary is equal to the hydrostatic pressure in the arteriole (Pa) that feeds the capillary. Therefore, Starling’s equation is simplified to

\[
\frac{J_v}{S} = \frac{L_p}{S} (P_a - \sigma P_i)
\]

determinations of Pa and plasma protein concentration (to estimate Pri) were made before and after L-NAME superfusion so that any changes in endothelial permeability (Lp or σ) could be detected: either an increase in Lp or a decrease in σ results in increased Jv/S.

Measurement of arteriolar pressure. Because hydrostatic pressure can affect measurements of capillary fluid filtration, Pa was measured with a servo-null apparatus (model 5A, Instrumentation for Physiology and Medicine, San Diego, CA). Micropipettes with a tip diameter <1 µm (Frederick Haer, Bowdoinham, ME) were filled with a 2 M NaCl solution containing 10 U/ml heparin. Penetration of the micropipette into the arteriole was facilitated with a micromanipulator. Pressure measurements were considered valid if there was a tight coupling with waveform of carotid arterial pressure and if there was no change in measurement with a small increase in gain.

Measurements from blood samples. Blood samples (400 µl) were taken during the baseline period and after I/R via the carotid arterial cannula, adding ~5 µl of 1,000 U/ml heparin to prevent coagulation. We mixed 50 µl of the blood with 10 µl of 1% crystal violet and 440 µl of 3% acetic acid and placed the resulting solution on a hemacytometer so that the number of neutrophils could be counted. The remainder of the blood sample was spun in a centrifuge, and 50 µl plasma were
drawn off and placed in a refractometer to measure plasma protein concentration. Osmostic pressure due to plasma protein was calculated with the equation developed by Gore (6).

L-NAME protocol. A 10- to 15-min stabilization period preceded withdrawal of a blood sample and baseline measurements of \( J / S \) and arterial pressure \( P_a \). After baseline measurements, the control BBS superfusion solution was replaced with 100 \( \mu \)M L-NAME (Bachem, Torrance, CA) dissolved in the control solution, and all measurements were repeated 20–25 min later. Three groups of animals underwent L-NAME superfusion: 1) control rats, 2) rats injected intraperitoneally with either a high dose (1 ml/kg) or a low dose (0.1–0.2 ml/kg) of ANS (Accurate Chemical and Scientific, Westbury, NY) 3 h before the initial anesthetic injection, and 3) rats injected intra-arterially with a monoclonal antibody against the leukocyte adhesion molecule CD18 [either 2 mg/kg Pharmacia-Upjohn Laboratories, Kalamazoo, MI, or 2 mg/kg WT.3 (see Ref. 27)].

Statistics. Two sets of data were compared with standard t-tests, and comparisons among more than two sets were made with Bonferroni’s post hoc test. Each test was performed with Instat software (GraphPad Software, San Diego, CA) using a 95% confidence level to determine significant differences. Data are presented as means ± SE.

RESULTS

Baseline capillary \( J / S \) in all groups averaged 0.015 ± 0.001 \( \mu \)m/s (n = 31; 2.3 ± 0.2 capillaries studied/rat). Figure 1 demonstrates that L-NAME increased \( J / S \), which is expressed as a relative value (1.66 ± 0.32; n = 11). \( J / S \) during the 20- to 25-min period of L-NAME superfusion was divided by \( J / S \) during the baseline period in each experiment. The surface area of the capillaries remained essentially constant based on the observation that capillary diameter changes did not exceed the microscope resolution of 0.5 \( \mu \)m. As indicated by the simplified Starling equation, \( J / S = L_p \left( P_a - \pi_c \right) \), the relative increase in \( J / S \) could be a result of altered permeability (an increase in hydraulic conductivity \( L_p \)) or a decrease in the osmotic reflection coefficient \( \sigma \) or a result of altered pressure (an increase in arteriolar hydrostatic pressure \( P_a \) or a decrease in plasma osmotic pressure \( \pi_c \)). To separate the effects of altered permeability from effects of altered pressure, \( P_a \) and \( \pi_c \) were determined in 11 rats with a servo-null apparatus and with plasma protein concentrations, respectively. The value of \( P_a \) decreased from 32.8 ± 1.8 to 28.4 ± 2.3 mmHg 20–25 min into L-NAME superfusion (P = 0.11), and \( \pi_c \) decreased from 14.7 ± 0.4 to 13.6 ± 0.4 mmHg (P < 0.05). Theoretical values of relative \( J / S \) in these experiments were calculated from \( P_a \) and \( \pi_c \), using the simplified Starling equation, assuming that there was no change in \( L_p \) and that \( \sigma \) remained constant at 0.9. For example, if \( P_a \) decreased from 32 to 28 mmHg and \( \pi_c \) decreased from 14 to 13 mmHg, relative \( J / S \) could be calculated by dividing \( L_p [28 - 0.9(13)] \) by \( L_p [32 - 0.9(14)] \). These calculated values of relative \( J / S \) (that assume no change in permeability) averaged 0.88 ± 0.13, which is significantly lower (P < 0.05) than the actual measurements of relative \( J / S \) (1.66 ± 0.32; Fig. 1). Therefore, the observed increase in \( J / S \) caused by L-NAME is due to increased capillary permeability rather than altered pressure gradients.

In the control group, eight measurements of \( P_a \) and \( \pi_c \) were made in the same rats as measurements of \( J / S \); in six other experiments, only \( P_a \) and \( \pi_c \) or \( J / S \) (n = 3 each) was measured. However, the same trends were present (decreased \( P_a \) and \( \pi_c \) and increased \( J / S \)) when measurements were made in the same or separate rats. One disadvantage of measuring both \( J / S \) and \( P_a \) and \( \pi_c \) measurements were difficult even without the added procedure of capillary occlusion. A second disadvantage of simultaneous measurements is the limitation of studying only one capillary per rat (the capillary at the branch point of an arteriole where \( P_a \) is measured). Therefore, in the remainder of the groups included in this study, \( J / S \) and \( P_a \) were measured in separate animals.

To determine the role of neutrophils in the capillary response to L-NAME, rats were injected with 1 ml/kg ANS, which reduced the number of circulating neutrophils to 92 ± 50 neutrophils/µl blood compared with 1,600 ± 282 neutrophils/µl blood (P < 0.05) in control rats. Both \( P_a \) and \( \pi_c \) remained near baseline values: 32.7 ± 1.7 mmHg during the baseline period and 32.0 ± 3.2 mmHg during L-NAME superfusion for \( P_a \) and 13.7 ± 0.4 to 13.7 ± 0.3 mmHg for \( \pi_c \) (n = 6 each). When the values of \( P_a \) and \( \pi_c \) are substituted into Starling’s equation, relative \( J / S \) would average 0.94 ± 0.12 if there were no change in permeability. However, as shown in Fig. 2, actual measurements of relative \( J / S \) in ANS-pretreated rats averaged 0.51 ± 0.12 (n = 5, P < 0.05 lower than calculated by pressure effects), indicating that L-NAME decreased capillary permeability. Therefore, in the presence of neutrophils, L-NAME causes increased permeability (Fig. 1), and in the absence of neutrophils L-NAME causes decreased permeability (Fig. 2). Injection of ANS did not alter baseline values of \( J / S \), which averaged 0.016 ± 0.002 \( \mu \)m/s compared with 0.013 ± 0.002 \( \mu \)m/s in untreated rats.

Studies of postcapillary venules have indicated that leukocyte-mediated increases in protein leakage are dependent on adhesive interactions between leuко-
cytes and endothelial cells. To determine if the mechanism of L-NAME-induced increases in capillary \( J / S \) includes leukocyte adhesion, an antibody against the adhesion molecule CD18 (CL26) was injected 5 min before L-NAME superfusion. Values of \( P_a, \pi_c \), measured in six rats were similar to the previous two groups, decreasing from 38.0 ± 1.4 to 35.0 ± 2.7 mmHg and from 16.0 ± 0.4 to 13.7 ± 0.4 mmHg (\( P < 0.05 \)), respectively. When values of \( P_a, \pi_c \) are substituted into Starling’s equation, relative \( J / S \) is estimated to average 0.96 ± 0.10, assuming no permeability change. However, as shown in Fig. 3, actual measurements of relative \( J / S \) in CL26-injected rats averaged 0.45 ± 0.16 (\( n = 6; P < 0.05 \) lower than calculated by pressure changes), which is similar to the results observed in ANS-pretreated rats (Fig. 2).

Conclusions based on the experiments using CL26 are complicated by the fact that the antibody caused partial neutropenia, −50% as effectively as when 1 ml/kg ANS was administered (see Fig. 4). Therefore, it was not possible to immediately conclude that the mechanism whereby neutrophils mediate L-NAME-induced increases in capillary \( J / S \) includes CD18. To clarify this issue, additional experiments were performed with a dose of ANS (0.1–0.2 ml/kg) that produced essentially the same level of neutropenia (640 ± 326 neutrophils/µl blood) as CL26 (717 ± 239), as shown in Fig. 4. In rats injected with the lower dose of ANS, L-NAME superfusion did not cause a decrease in \( J / S \) as in the CL26 group (Fig. 3). Additionally, the CL26 results were confirmed in four rats injected with WT.3, another CD18 monoclonal antibody, which in contrast to CL26 does not cause neutropenia. With WT.3 injected, L-NAME-induced \( J / S \) decreased significantly (\( P < 0.05 \)) to an average of 0.63 ± 0.10. Therefore, the decrease in \( J / S \) during L-NAME superfusion in the CL26 group was not merely an effect of partial neutropenia.

**DISCUSSION**

Over the past few years, NO has drawn much interest in several fields of biomedical research. Of particular interest to microcirculation researchers, NO helps control arteriolar tone and thus the rate of blood and oxygen delivery to the capillaries. On the opposite side of the microvasculature in the postcapillary venules, NO has been shown to be a protective agent, at least in certain models of inflammation, preventing leukocyte-endothelial cell interactions and protein leakage. A region of the microcirculation that has not received due attention with respect to the role of NO is the capillary bed. This study invokes an essential role for NO in maintaining the capillary barrier to fluid filtration and is the first study to demonstrate that capillary permeability changes induced by NO synthase inhibition can be reversed in the absence of neutrophils. In the presence of neutrophils, L-NAME was shown to have a proinflammatory effect, increasing capillary \( J / S \) by 66%. However, during ANS-induced neutropenia, L-NAME was shown to have an anti-inflammatory effect, decreasing \( J / S \) by ~50%. The present study further showed that the mechanism whereby neutrophils are involved in the L-NAME-mediated response includes the adhesion molecule CD11/CD18, as indicated by a decrease in \( J / S \) by 55% with an antibody against CD18.

Despite the scarcity of information on the effect of NO on capillaries, this is not the first investigation of the effect of NO synthase inhibition on capillary permeabil-

![Fig. 2. Effect of L-NAME on relative J /S when rats were pretreated with a high dose (1 ml/kg) of antineutrophil serum (ANS). The filled bar gives actual measurements of relative J /S, and the open bar gives calculation of J /S assuming no permeability change, using measurements of arteriolar pressure and plasma protein concentration. Data are given as means ± SE; *P < 0.05 compared with pressure effects for CL26.](http://ajpgi.physiology.org/)

![Fig. 3. Effect of L-NAME on relative J /S when rats were pretreated with a CD18 monoclonal antibody (CL26) or with 0.1–0.2 ml/kg ANS (low-dose ANS). Filled bars give actual measurements of relative J /S, and the open bar gives calculation of J /S assuming no permeability change, using measurements of arteriolar pressure and plasma protein concentration in CL26 protocol. Data are given as means ± SE; *P < 0.05 compared with pressure effects for CL26.](http://ajpgi.physiology.org/)

![Fig. 4. Circulating neutrophil (PMN) counts in control L-NAME group compared with groups pretreated with a high dose of ANS (1 ml/kg), a low dose of ANS (0.1–0.2 ml/kg), and a CD18 monoclonal antibody (CL26). Data are given as means ± SE; *P < 0.05 compared with control L-NAME group.](http://ajpgi.physiology.org/)
ity. Rumbaut et al. (24) studied the effect of another NO synthase inhibitor, L-NMMA, on permeability of capillaries in the frog mesentery. They found that L-NMMA caused a significant decrease in capillary hydraulic conductivity that was reversed by a 100-fold excess concentration of L-arginine (a precursor of NO). Furthermore, L-arginine alone also caused a significant increase in hydraulic conductivity. These results do not necessarily conflict with the present study, as their protocol of measuring hydraulic conductivity does not include the presence of leukocytes. The importance of the present study is the novel demonstration that the effect of NO synthase inhibition on capillary permeability is critically dependent on the presence of neutrophils.

The present study took an additional step past the demonstration of neutrophil involvement in the capillary response to L-NAME by showing that the mechanism includes the neutrophil adhesion molecule CD11/CD18. This molecule has been demonstrated to play a key role in several models of acute inflammation. For example, monoclonal antibodies against CD11/CD18 have been shown to prevent injury after I/R (2, 11, 12), including an intravital microscopy study that showed attenuation of I/R-induced increases in protein leakage from postcapillary venules (14). In the same model of I/R, postcapillary protein leakage was also attenuated by increasing the availability of NO (17). Using this model, Kurose et al. (15) have also established a link between the availability of NO and CD18-mediated protein leakage. Kurose et al. (15) have demonstrated that the level of L-NAME-induced protein leakage is related to the number of firmly adherent leukocytes in postcapillary venules and that protein leakage is attenuated with the CD18 monoclonal antibody CL26. However, CD18-mediated increases in vascular permeability are not limited to the site of firmly adherent leukocytes (postcapillary venules). The present study demonstrates that CD18 also plays a critical role in the way in which neutrophils affect capillary permeability after exposure to L-NAME.

It should be noted that two other studies of L-NAME induced increases in vascular permeability (13, 15) have demonstrated an attenuation, but not a reversal, of permeability changes with CD18 monoclonal antibodies. One of these studies (15) looked exclusively at the response in postcapillary venules, and the other (13) was a whole organ study. It is possible that the absence of a reversal in permeability changes in their studies represents a difference between capillaries and venules or between diffusive protein leakage and convective fluid leakage.

The observation in the present study that neutrophil adhesion is involved in the capillary response to L-NAME presents an interesting question of how neutrophils affect permeability of these small vessels. Neutrophil adhesion is essentially confined to postcapillary venules, with no firm adherence present in any capillaries included in this study. Even so, attenuation of neutrophil adhesion with ANS and CL26 had dramatic effects on the capillary response to L-NAME.

Similar observations have been made in the rat mesentery using another model of acute inflammation (8, 9), superfusion of PAF. In the PAF model (8, 9), increases in capillary J\textsubscript{w}/S were attenuated by administration of antibodies inhibiting leukocyte rolling (with sialyl-Lewis\textsuperscript{x}) and with a P-selectin monoclonal antibody and leukocyte firm adherence (with CL26). The fact that leukocyte adhesion is involved in the response of capillaries during acute inflammation presents the possibility that there is a communicated response between postcapillary endothelium and capillary endothelium as suggested previously (7). The communication could be in the form of 1) a propagated signal delivered by adjacent endothelial cells through gap junctions (4, 25) from the site of postcapillary neutrophil adhesion upstream to the capillaries, 2) diffusion of mediators produced at the site of postcapillary neutrophil adhesion through the interstitium and reaching the capillaries, or 3) recirculation of mediators produced at the site of postcapillary neutrophil adhesion back to the arterial system, where they are delivered to the capillaries.

In summary, the present study helps to clarify the role that NO plays in capillary permeability to fluid. In the presence of neutrophils, NO synthase inhibition was shown to increase capillary J\textsubscript{w}/S, whereas during neutropenia and during inhibition of leukocyte adherence, L-NAME was shown to decrease capillary J\textsubscript{w}/S. Therefore, in the physiological setting of neutrophil-perfused vessels, it appears that NO can provide protection against increased capillary permeability during acute inflammation.

I acknowledge Bill Shively for skillful technical assistance and Dr. D. N. Granger for insight and critical evaluation of the manuscript.

This work was supported by National Heart, Lung, and Blood Institute Grant HL-55255 and by a grant from the Biomedical Research Foundation of Northwest Louisiana.

Address reprint requests to Dept. of Physiology, Louisiana State Univ. Medical Center, 1501 Kings Hwy., Shreveport, LA 71130-3932.

Received 18 February 1997; accepted in final form 29 August 1997.

REFERENCES


