Leukocyte–Endothelium Interaction in the Rat Mesenteric Microcirculation during Halothane or Sevoflurane Anesthesia

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Background: The effects of inhalational anesthetics on the microcirculation, including leukocyte dynamics, remain to be clarified. The authors investigated halothane and sevoflurane anesthesia to determine if these agents evoked leukocyte adhesion through endothelial cell-dependent mechanisms involving such adhesion molecules.

Methods: Rats were anesthetized with halothane or sevoflurane in 100% oxygen and the lungs were mechanically ventilated. Leukocyte behavior in mesenteric venules was recorded through intravital video microscopy under monitoring microvascular hemodynamics. To examine the mechanisms for leukocyte rolling and adhesion, these studies were repeated after animals were pretreated with a monoclonal antibody against P-selectin (MAB PB1.3) or against intracellular adhesion molecule-1 (ICAM-1; MAB 1A29); P-selectin required for rolling of circulating leukocytes and ICAM-1 for firm adhesive interactions with leukocyte integrins.

Results: Under baseline anesthetic conditions (1 minimum alveolar concentration [MAC]), venular wall shear rates, an index of the dispersive force on marginating leukocytes, in the sevoflurane-treated rats were about two times higher than those with halothane. At 2 MAC, halothane caused a marked arteriolar constriction and decreasing shear rates concurrent with an increasing density of venular leukocyte adhesion. Sevoflurane at 2 MAC induced leukocyte rolling and adhesion, which were attenuated by PB1.3 and 1A29, without alterations in the wall shear rates. Halothane-induced leukocyte adhesion was not prevented by PB1.3 but it was by 1A29.

Conclusions: Halothane or sevoflurane anesthesia induces venular leukocyte rolling and adhesion: P-selectin upregulation plays a crucial role in leukocyte rolling and adhesion during sevoflurane anesthesia, whereas low-flow perfusion is likely to evoke ICAM-1–dependent leukocyte adhesion during halothane anesthesia. (Key words: Anesthesia, inhalational. Blood, leukocyte. Pharmacology: nitric oxide; P-selectin; intracellular adhesion molecule-1.)

DURING the early process of inflammation, leukocytes exhibit rolling along the venular endothelium. This phenomenon limits the population of adherent and migrating leukocytes accumulated in the inflamed tissue and thereby serves as a determinant of inflammatory responses.1,2 Evidence was recently published that the endothelial cell-dependent adhesion mechanisms involve at least two distinct adhesion molecules; P-selectin, which is required for circulating leukocytes to roll along postcapillary venules,3 and intracellular adhesion molecule-1 (ICAM-1), a ligand molecule for leukocyte integrins that is necessary to establish firm adhesion and migration of leukocytes.4 The present study was designed to examine a hypothesis that inhalational anesthesia activates such endothelial cell-dependent mechanisms for leukocyte adhesion. To this end, using intravital observation of the rat mesenteric microcirculation, the effects of two inhalational anesthetics, halothane and sevoflurane, on leukocyte–endothelial cell interaction were examined under monitoring microvascular hemodynamics.

Materials and Methods

Our study protocol was approved by the Animal Care and Utilization Committee, Keio University School of
Male Wistar rats were maintained in an animal care facility in accordance with National Institutes of Health guidelines. They were fed ad libitum with water and laboratory chow until the experiments, when their weights ranged from 300 - 350 g.

**Experimental Protocol**

After anesthesia was induced with either halothane (1.5 - 2.0%) or sevoflurane (2.5 - 3.0%) in 100% oxygen, rats were placed supine on a surgical board. After tracheostomy, the rat lungs were mechanically ventilated with a Harvard ventilator for small animals (model 683, South Natick, MA). The right carotid artery was cannulated with a 24-gauge polyethylene catheter connected to a pressure transducer (Prezact II; Terumo, Tokyo, Japan) to monitor mean arterial pressure. Expiratory concentrations of inhalational anesthesia were continuously monitored by an anesthesia gas analyzer (Ohmeda 5250RG; BOC Health Care, Louisville, CO). The abdomen was opened via a midline incision. The ileocecal portion of the mesentery was carefully exposed and mounted on a plastic support for intravital microscopy, as previously described. The preparation was kept at 37°C and continuously superfused (1 ml/min) with Krebs-Henseleit bicarbonate-buffered solution saturated with a 95% nitrogen and 5% carbon dioxide gas mixture.

**Monitoring of Microvascular Changes in Vivo**

The mesenteric microcirculation was visualized through intravital video microscopy (magnification, ×90) as described previously. After stabilization of the mesentery during 1 minute alveolar concentration (MAC), straight and unbranched precapillary arterioles and postcapillary venules (25 - 35 μm in diameter) were chosen for observation. A 10-min recording during 1 MAC inhalation (halothane 0.7%, n = 6; sevoflurane 1.7%, n = 6) was done to evaluate the baseline leukocyte rolling and adhesion in venules. Arteriolar and venular diameters, the number of adherent leukocytes, and leukocyte rolling velocity (Vw) in venules were determined off-line by playing back of the videotaped images. The Vw was determined as the time required for a leukocyte to transverse a given length of venule, as described previously. Adherent leukocytes were defined as those adhering to venular endothelium for more than 30 s, and the density of adherent leukocytes was expressed as the number of cells per 100-μm length of venules observed. The centerline erythrocyte velocity (Ve) was measured using a temporal correlation velocimeter (IPM Inc., San Diego, CA) as described elsewhere. Because 2 MAC halothane caused a remarkable depression of Vw in the mesenteric microcirculation that could not be measured by the temporal correlation velocimeter, we also used a high-speed video camera (Ektapro 2000, Kodak, San Diego, CA) to precisely examine the Vw values in microvessels during halothane anesthesia by visualizing the movement of the erythrocyte movement. Simultaneously, since a marked reduction of Vw during 2 MAC halothane anesthesia was observed during individual erythrocytes and interfered with an optical quality of imaging for the leukocyte rolling, we did not measure Vw of leukocytes.

As a hemodynamic parameter changing as a function of the force of rolling leukocytes, venular wall shear rates (r) were calculated using the formula: r = (V_m / D), where V_m is erythrocyte velocity/1.6 and D is venular diameter. The inhalational concentration of each anesthetic was increased up to 1.5% for halothane or 3.4% for sevoflurane. After the 20-min stabilization period, the recordings were repeated. To examine the reversibility of the anesthetic effects, the parameters noted before were measured 20 min after reducing the dose of anesthesia to 1 MAC. Then the rats were killed with an injection of pentobarbital.

**Interventions**

In a separate set of experiments, rats anesthetized with halothane or with sevoflurane were pretreated with sodium nitroprusside (SNP), with a monoclonal antibody against P-selectin (murine immunoglobulin G1 anti-P-selectin monoclonal antibody, MAb PB1.3, 2 mg/kg, provided by Sumitomo Pharmaceutical Co., Osaka, Japan) or with a monoclonal antibody against ICAM-1 (murine immunoglobulin G1 anti-ICAM-1 monoclonal antibody, 1A29, 1 mg/kg, a generous gift from Professor Masayuki Miyasaka, Osaka University School of Medicine); SNP was superfused on the mesentery at 0.1 μM, and PB1.3 and 1A29 were given intravenously. When necessary, a nonbinding murine immunoglobulin was administered intravenously at 2 mg/kg as a control experiment. Because the systemic administration of SNP modified venular wall shear rates, possibly confusing interpretation of the results, SNP was superfused on the mesentery directly. These interventions were performed after completing the recording of baseline microvascular parameters and were followed by the 10-min video recording before the increase in the dose of anesthetics. Then the inhalational concentration of halothane or sevoflurane was increased to 2 MAC, when the measurements were repeated twice every 10 min.
Visualization of Microvascular Expression of P-selectin in Vivo

In the next series of experiments, expression of P-selectin in the rat mesenteric microcirculation in vivo was examined using laser confocal fluorescence video microscopy (LSM-GB200, Olympus, Tokyo, Japan). A monoclonal antibody (PB1.3) was labeled with fluorescein isothiocyanate (FITC) and the fluorescence binding was confirmed before use as described previously. The ileocecal portion of the mesentery was mounted on a plastic stage and superfused with the Krebs-Henseleit solution as described in Materials and Methods. The mesenteric microcirculation was observed through an inverted-type microscope (TDM-300, Nikon, Tokyo, Japan) equipped with an oil-immersion fluorescence objective lens (×40, Nikon, Tokyo, Japan) and was epifluorescently at 488 nm using an Argon laser light source. The fluorescent confocal images passing through a 535-nm pass filter were visualized using a line-scan confocal imaging unit (InSight, Melidian Instruments, Okemos, MI) and a silicon intensified target camera under the fixed conditions of contrast enhancement (gain 4, offset 2). These procedures allowed us to obtain the optimal dynamic range to determine the local intensity of fluorescence associated with the specific binding of PB1.3 to P-selectin expressed on the mesenteric microvessels. The width of the confocal plane along the z axis was set at 4 μm. The FITC-labeled PB1.3 was injected from the femoral vein at a dose of 0.5 mg/kg after completing the 20-min stabilizing period under 1 MAC anesthesia. After the 5-min incubation period, the concentration of sevoflurane or halothane was increased to 2 MAC. The P-selectin–associated fluorescence images were recorded before and every 5 min after the elevation of anesthetic concentrations. Time exposure to visualize the P-selectin expression was limited within 2 s using an electric shutter controller (Sankei Inc., Tokyo, Japan) to avoid unnecessary light exposure and possible photobleaching. Microvascular images were digitally introduced into an image-analyzing computer (Image 1.58/Macintosh, Apple Computers, Cupertino, CA). This system allowed us to average individual images and to help reduce background noise. In the current experiments, eight sequential images were averaged to establish a single fluorograph for fluorescence measurements.

Using the FITC-labeled MAb, the ratio between the intensity of fluorescence and that of IgG was estimated in advance. To calibrate the fluorescence intensity in microfluorographs in vivo, the Krebs-Henseleit solution containing varied concentrations of FITC was placed on the stage of the microscope to obtain the standard fluorescent images. These images were used to establish the relation between the MAb concentrations (approximately 0.1 μM and 2 μM) and gray levels of the micrographs. Assuming that the light transparency of the mesenteric tissue is the same as that of the buffer solution, the fluorescence gray levels measured at microvascular walls were transformed to the corresponding concentrations of FITC before and after each anesthesia, based on the calibration curve, and were expressed as apparent concentrations, as described elsewhere.

Data Analysis

The data were expressed as mean ± SEM unless otherwise specified. Multiple analysis of variance with repeated measurements was used to examine the results over the study periods. If an overall difference was detected, Bonferroni-corrected pair-wise comparisons were made. In the study of intravital P-selectin visualization, the fluorimetric data collected from 20 different sites in postcapillary venules were analyzed by Student’s t test before and after setting the anesthetic concentration to 2 MAC as paired values collected from the same animal preparation. Probability values less than 0.05 were considered significant.

Results

Arteriolar Constriction and Venular Leukocyte Adhesion by Anesthetics

Figure 1 illustrates the effects of halothane and sevoflurane on macro- and microcirculatory hemodynamic parameters such as mean arterial pressure, arteriolar diameter, and VR in arterioles (n = 6 for each group). During the baseline period under 1 MAC anesthesia, there were no fundamental differences in these parameters between the halothane- and sevoflurane-treated groups. When the dose of anesthetic was increased to 2 MAC, the extent of the arterial pressure decrease was slightly greater in the rats treated with halothane than in those treated with sevoflurane, although the mean arterial pressure value showed a significant decrease in both groups. In addition, the microvascular beds during 2 MAC of halothane exhibited a marked constriction of arterioles accompanied by a significant reduction of the VR, whereas the compatible dose of sevoflurane did not evoke any significant changes in these parameters. When the halothane concentration was returned to 1
MAC, all three parameters were still reduced compared with the baseline values. However, the mean arterial pressure in sevoflurane-treated rats was fully recovered in response to the reduction of the concentration.

Differences in microvascular responses between the two anesthetics were also revealed in the adhesive interaction between leukocytes and the venular endothelium. During the initial 1-MAC period, the basal density of adherent leukocytes was two times greater in the halothane-treated group than in the sevoflurane-treated group (table 1). With the increase to 2 MAC, the adhesion density increased further in both groups. However, when the anesthetic concentration was returned to 1 MAC, the adhesion density in the sevoflurane group, but not that in the halothane group, was reduced to the baseline level (table 1).

### Halothane Induces Shear-dependent Leukocyte Adhesion

Figure 2 illustrates time history of the density of adherent leukocytes and venular shear rates during halothane anesthesia and the effects of SNP (n = 4), PB1.3 (n = 4), and 1A29 (n = 3) on these parameters. Under the baseline conditions (1 MAC), the venular shear rates were as low as 200 s⁻¹, which is 50% of the baseline values measured in the same mesenteric venules under pentobarbital anesthesia, as described elsewhere. Pretreatment with SNP, PB1.3, or 1A29 did not cause any significant changes in the density of adherent leukocytes and wall shear rates at 1 MAC. In response to the increase in halothane concentration to 2 MAC, the density of adherent leukocytes was increased significantly, which coincided with a depression of venular shear rates. Pretreatment with PB1.3 did not ameliorate the halothane-induced leukocyte adhesion and reduction of the shear rates. Administration of 1A29 did not decrease the Vₕ but did attenuate the density of adherent leukocytes. The superfusion with SNP prevented the increase in leukocyte adhesion without reversing the decreasing wall shear rates.

### Sevoflurane Induces Leukocyte Adhesion without Altering Venular Shear Rates

Figure 3 shows alterations in leukocyte adherence and venular shear rates during sevoflurane anesthesia. Under the baseline conditions, the venular shear rates were greater than 400 s⁻¹, which was twice as high as those in the halothane-treated rats. Leukocyte adherence and wall shear rates did not change significantly by pretreatment with SNP, PB1.3, or 1A29 under 1 MAC sevoflurane anesthesia. When the sevoflurane concentration increased

Table 1. The Number of Adhered Leukocytes in Postcapillary Venules during Halothane or Sevoflurane Anesthesia

<table>
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<th>1 MAC (baseline)</th>
<th>2 MAC</th>
<th>1 MAC (recovery)</th>
</tr>
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<tbody>
<tr>
<td>Halothane</td>
<td>5.2 ± 0.9</td>
<td>15.1 ± 2.1*</td>
<td>9.0 ± 0.9†</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>2.50 ± 1.12</td>
<td>10.8 ± 3.0*</td>
<td>2.50 ± 1.01</td>
</tr>
</tbody>
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Values are mean ± SEM (leukocytes/100 μm postcapillary venules).

MAC = minimum alveolar concentration; 1 MAC = halothane 0.7% versus sevoflurane 1.7%.

* P < 0.01 versus 1 MAC (baseline).

† P < 0.05 versus 1 MAC (baseline).
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to 2 MAC, the density of adherent leukocytes was elevated approximately four times compared with the baseline, whereas the venular shear rates exhibited no significant reduction. The sevoflurane-induced venular leukocyte adhesion was significantly attenuated by pretreatment with SNP (n = 5), with PB1.3 (n = 5), or with 1A29 (n = 4). Nonbinding IgG (n = 4) did not modify the sevoflurane-elicited changes in leukocyte behavior.

Involvement of P-selectin in Leukocyte Rolling during Anesthesia

The observation indicating the blockade of sevoflurane-induced leukocyte adhesion by PB1.3 prompted us to try to determine whether sevoflurane influences leukocyte rolling kinetics in venules. Figure 4 illustrates the time history of the $V_w/N_R$ normalized by the centerline erythrocyte velocity ($V_w/N_R$) during sevoflurane anes-

![Graph 1](image1)

Fig. 1. Leukocyte adherence and wall shear rates during sevoflurane anesthesia. $V_w/N_R$ = venular wall shear rate; $V_w$ = venular velocity; $N_R$ = reference velocity; $V_w/N_R$ = normalized wall shear rate. *$P < 0.05$ for the 20-min study period (1 MAC); **$P < 0.05$ for the halothane group.

![Graph 2](image2)

Fig. 2. Leukocyte adherence and wall shear rates during halothane anesthesia. SNP = sodium nitroprusside; Mab PB1.3 = monoclonal antibody against P-selectin; Mab 1A29 = monoclonal antibody against intracellular adhesion molecule-1; MAC = minimum alveolar concentration. The shaded area denotes the period when rats were treated with 2 MAC anesthesia. *$P < 0.05$ and **$P < 0.01$ for the 20-min study period (1 MAC); ***$P < 0.05$ for the halothane group.

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![Graph 3](image3)

Fig. 3. Leukocyte adherence and wall shear rates during sevoflurane anesthesia. SNP = sodium nitroprusside; Mab PB1.3 = monoclonal antibody against P-selectin; Mab 1A29 = monoclonal antibody against intracellular adhesion molecule-1; IgG = nonbinding immunoglobulin; MAC = minimum alveolar concentration. *$P < 0.05$ for the 20-min study period (1 MAC); **$P < 0.05$ for the sevoflurane group.

The effects of pretreatment with SNP, PB1.3, or 1A29. Under baseline conditions (1 MAC), the mean $V_w/N_R$ values were 3.4%. Treatment with SNP or PB1.3 showed a slight increase in $V_w/N_R$ during 1 MAC sevoflurane anesthesia (+13% and +33%, respectively) but was not statistically significant. In response to an increase in the sevoflurane concentration to 2 MAC, the $V_w/N_R$ values exhibited a significant decrease, indicating the increase in the adhesion force between leukocytes and venular endothelium. The sevoflurane-induced increase in the $V_w/N_R$ values was reversible, inasmuch as the reduction in sevoflurane concentration to 1 MAC reversed the $V_w/N_R$ values to baseline levels (data not shown). Pretreatment with SNP or with PB1.3, but not
with 1A29 or nonbinding IgG, significantly attenuated the sevoflurane-induced reduction in the $V_s/V_r$ values.

To confirm the involvement of P-selectin in the anesthesia-induced leukocyte rolling and adhesion, we did laser confocal microfluorographic examinations to demonstrate P-selectin expression on venular endothelium in vivo (fig. 5). Under the baseline 1 MAC sevoflurane anesthesia, most of the fluorescence was observed in the intravascular lumen, and only a little staining could be detected along the microvascular wall (fig. 5B). In response to the elevation in sevoflurane concentration, the microvascular lining was highlighted with an increase in the PB1.3-associated fluorescence as early as 5 min after 2 MAC anesthesia was established (fig. 5C). Administration of FITC-labeled nonbinding mouse IgG did not evoke such a site-specific increase in fluorescence. Similarly, during halothane anesthesia, comparable results were obtained when its concentration was increased from 1 MAC to 2 MAC. The intensity of fluorescence on the venular wall was increased significantly in both groups (0.66 ± 0.16 μm vs. 0.95 ± 0.24 μm in the sevoflurane-treated group and 0.70 ± 0.15 μm vs. 1.02 ± 0.22 μm in the halothane-treated group; $P < 0.01$).

**Discussion**

The present results indicate that inhalational anesthesia with halothane or sevoflurane causes a significant

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Fig. 4. Distribution of the rolling velocity ($V_s/V_r$) ratio during sevoflurane experiments. SNP = sodium nitroprusside; MAb 1.3 = monoclonal antibody against P-selectin; MAb 1A29 = monoclonal antibody against intracellular adhesion molecule 1; IgG = nonbinding immunoglobulin; MAC = minimum alveolar concentration. $P < 0.05$ for the 20-min study period (1 MAC); $P < 0.05$ for the sevoflurane group.

Fig. 5. P-selectin expression in the rat mesenteric microvessels during sevoflurane anesthesia. (A) A transillumination micrograph of microvessels, $a$ = arteriole, $v$ = venule; the bar represents 20 μm. (B) A fluorescence image recorded in the same microscopic field 5 min after the injection of FITC-labeled monoclonal antibody against P-selectin (PB1.3) during the baseline period under 1 minimum alveolar concentration (MAC) anesthesia. Most of the fluorescence was observed in the intravascular lumen, indicating the presence of the circulating monoclonal antibody. (C) A microfluorograph in the same field during 2 MAC sevoflurane anesthesia. The image was recorded 10 min after the increase in sevoflurane concentration to 2 MAC. Fluorescence intensity increased specifically on the venular walls, displaying greater levels of the FITC binding PB1.3 in the venules than those observed during 1 MAC anesthesia.
increase in leukocyte rolling and adherence in the postcapillary venules of the rat mesentery. Such a leukocyte-endothelial cell interaction including "firm adhesion" of leukocytes has been proposed as a key event in the evolution of tissue or organ injury.\(^1\)\(^2\) Therefore, the current study suggests the possibility that a high concentration of inhalational anesthesia \textit{per se} predisposes leukocyte-dependent organ injury after surgery.

Although an increasing dose of both anesthetics causes venular leukocyte adhesion, microvascular hemodynamics exhibited different features between the two anesthetics: Halothane markedly constricted arterioles and reduced the erythrocyte velocity, thereby causing a low-flow state or "to-and-fro" patterns in the distal venules at 2 MAC. Under such low-flow conditions, multiple factors, such as a reduction of wall shear rates\(^3\) and ischemia-reperfusion\(^4\) in regional microvessels, are likely to be involved in the mechanisms of leukocyte adhesion. Despite decreasing the dose of halothane, the impairment of the arteriolar hemodynamics and the increase in leukocyte adhesion were not completely recovered, indicating a sparse reversibility of the microvascular responses during halothane anesthesia. In contrast, sevoflurane did not cause any serious deterioration in microvascular hemodynamics. This anesthetic preserved the arterial tone and microvascular erythrocyte velocity to a greater extent than did halothane. The difference in the stability of arteriolar tone between sevoflurane and halothane revealed by the current study \textit{in vivo} is comparable to the previous observation that sevoflurane anesthesia had minimal effects on systemic hemodynamics while halothane markedly depressed them.\(^5\) Further, the sevoflurane-induced venular leukocyte adhesion was fully reversed within 20 min after decreasing its concentration back to 1 MAC.

These different features of microvascular hemodynamics seem to provide a distinct spectrum of adhesion molecules responsible for the venular leukocyte adhesion hemodynamics in sevoflurane and halothane anesthesia. Specifically, sevoflurane-induced leukocyte adhesion is likely to result from shear rate-independent mechanisms that function even under the "physiologic" shear rates. It was previously shown that adhesion molecules such as selectins are required for leukocyte rolling and adhesion under the physiologic shear rates.\(^6\)\(^7\)\(^8\) The current study showed that the P-selectin-dependent adhesion mechanism plays a crucial role in sevoflurane-induced leukocyte sequestration \textit{in vivo}. Recent data have provided considerable evidence that oxygen-derived free radicals are potential mediators for P-selectin expression on endothelial cells.\(^6\) In this context, other evidence has been provided that sevoflurane serves as a direct source of superoxide anions.\(^9\) In addition, it recently has been documented \textit{in vivo} that endogenous nitric oxide (NO) suppression enhances hydroperoxide formation in microvascular endothelium and thereby enhances P-selectin-dependent venular leukocyte recruitment.\(^6\) Given these findings, such actions of sevoflurane may help enhance intracellular oxidant formation directly or indirectly and thereby upregulate subsequent P-selectin-dependent leukocyte adhesion in the postcapillary venules. Moreover, our observation showing that the blockade of adhesion changes by anti-ICAM-1 monoclonal antibody collectively supports a concept that two-step adhesive mechanisms involving selectin and integrins are required for leukocyte adhesion during sevoflurane anesthesia.

The leukocyte adhesion elicited by halothane, which caused a marked reduction in shear rates, seems to depend exclusively on the ICAM-1-mediated mechanism, and P-selectin had little, if any, involvement. However, the results of the immunohistochemistry study indicate that, as with sevoflurane, halothane induces P-selectin upregulation on microvascular endothelium. Low-flow states such as hemorrhagic shock cause shear-dependent leukocyte adhesion,\(^10\) and thus potent depressive effects of halothane on microcirculatory hemodynamics likely overcame such molecular changes of microvascular endothelial cells. These events associated with 2 MAC halothane anesthesia are not surprising in light of a previous report showing that low-shear-dependent leukocyte adhesion is mediated by ICAM-1 but not by P-selectin.\(^11\) Once the disperse force on circulating leukocytes is decreased by a reduction of venular wall shear rates, these cells could readily interact with ICAM-1, which is constitutively expressed on the surface of the microvascular endothelial cells,\(^11\) and thus confirm stationary adhesion independent of P-selectin.

Exogenously applied NO attenuated leukocyte adhesion elicited by sevoflurane and by halothane. There is an increasing body of evidence that NO serves as an "anti-adhesive" reagent through its biologic actions, such as cancellation of superoxide anions,\(^12\)\(^13\) downregulation of P-selectin-dependent leukocyte adhesion,\(^7\) and inhibition of reduced nicotinamide adenine dinucleotide phosphate oxidase, the superoxide-generating system in neutrophils.\(^14\) These experimental data lead us to hypothesize that inhalational anesthetics enhance oxidative stress in microvessels through their in-
hibitory action on the ability of endothelial cells to produce NO, as shown previously in vivo. We could not provide direct evidence showing the actual reduction of NO generation in situ. In addition, it remains to be clarified if acceleration of venular leukocyte adhesion by endogenous NO suppression may jeopardize the viability of organs in anesthetized hosts.

In conclusion, a high inhalational concentration of halothane or sevoflurane anesthesia induces venular leukocyte rolling and adhesion: P-selectin upregulation plays a crucial role in the leukocyte rolling and adhesion during sevoflurane anesthesia, whereas low shear rates are likely to evoke ICAM-1-dependent leukocyte adhesion during halothane anesthesia.

References