RAPID COMMUNICATION

Fluid Shear Stress Modulates Surface Expression of Adhesion Molecules by Endothelial Cells

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We investigated the effect of hemodynamic shear forces on the expression of adhesive molecules, E-selectin, and intercellular adhesion molecule-1 (ICAM-1) on human umbilical vein endothelial cells (HUVEC) exposed to laminar (8 dynes/cm²) or turbulent shear stress (8.6 dynes/cm² average), or to a static condition. Laminar flow induced a significant time-dependent increase in the surface expression of ICAM-1, as documented by flow cytometry studies. Endothelial cell surface expression of ICAM-1 in supernatants of HUVEC exposed to laminar flow was not modified, excluding the possibility that HUVEC exposed to laminar flow synthesize factors that upregulate ICAM-1. The effect of laminar flow was specific for ICAM-1, while E-selectin expression was not modulated by the flow condition. Turbulent flow did not affect surface expression of either E-selectin or ICAM-1. To evaluate the functional significance of the laminar-flow–induced increase in ICAM-1 expression, we studied the dynamic interaction of total leukocyte suspension with HUVEC exposed to laminar flow (8 dynes/cm² for 6 hours) in a parallel-plate flow chamber or to static condition. Leukocyte adhesion to HUVEC pre-exposed to flow was significantly enhanced, compared with HUVEC maintained in static condition (233 ± 67 v 43 ± 16 leukocytes/mm², respectively), and comparable with that of interleukin-1β treated HUVEC. Mouse monoclonal antibody anti–ICAM-1 completely blocked flow-induced upregulation of leukocyte adhesion. Interleukin-1β, which upregulated E-selectin expression, caused leukocyte rolling on HUVEC that was significantly lower on flow-conditioned HUVEC and almost absent on untreated static endothelial cells. Thus, laminar flow directly and selectively upregulates ICAM-1 expression on the surface of endothelial cells and promotes leukocyte adhesion. These data are relevant to the current understanding of basic mechanisms that govern local inflammatory reactions and tissue injury.

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ENDOTHELIAL CELLS play an active role in the processes of leukocyte adhesion to vascular wall and their subsequent extravasation into inflamed tissue.4-13 Molecules expressed on the surface of endothelial cells involved in the endothelial cell-leukocyte interaction have been recently identified and their specific role is being investigated.4 Stable adhesion of leukocytes to vascular endothelium is consistently preceded by their rolling on the vessel inner surface as a result of a dynamic equilibrium between the tractive forces induced by the flow of blood and the resistance opposed by the endothelial cell surface. The complex phenomenon of cell rolling on the endothelium involves a weak interaction between adhesion molecules on the surface of endothelial cells and counter-receptors on the surface of adhering leukocytes. Such an event implies a continuous process of binding to and detachment of circulating cells from the endothelial surface that allows leukocytes to roll more slowly than freely circulating cells. Molecules involved in this process appear to belong to the family of selectins,6-10 in which E-selectin, newly expressed on the endothelial cell surface upon cytokine activation,11 plays a pivotal role. While rolling, occasional leukocytes stop, remaining in contact with the endothelial surface and firmly adhere to it.4 Stable adhesion involves endothelial cell activation with consequent upregulation of a number of molecules belonging to the Ig gene superfamily, constitutively expressed on the endothelial surface.13 Upregulation of these molecules serves to bind their natural counter-receptor on circulating cells. Thus, endothelial intercellular adhesion molecule-1 (ICAM-1) binds the β2 integrin counter-receptor CD11b-CD18 on activated neutrophils, driving the subsequent process of leukocyte transmigration.15,14

Hemodynamic flow conditions have a major influence on the process of leukocyte adhesion to endothelium in vivo.5,17 Specifically, the flow velocity gradient near the vessel wall induces tractive forces (shear stress) tangential to the endothelial cell surface that oppose leukocyte adhesion. The effects of flow on leukocyte-endothelial interaction have been mimicked in vitro using parallel-plate perfusion chambers and videomicroscopy.18,19 However, leukocyte adhesion in vivo and in vitro differs greatly because adhesion can take place at much higher shear stress levels in vivo (up to 30 dynes/cm²) than in vitro (<5 dynes/cm²).18,19,20,22 The reason for this is not yet known. Aside from affecting the interaction between circulating cells and the endothelial surface, mechanical forces induced by the blood flow (ie, hydraulic pressure and flow velocity) directly modulate the structure and function of vascular endothelial cells.20,22 Because fluid shear stress regulates a genetic program that alters the synthesis and release of endothelial cell molecules, the possibility has been explored that changes in flow conditions on the endothelial cells influence the surface expression of leukocyte adhesion molecules. Recent results indicated that laminar flow (10 dynes/cm²) increases the expression of ICAM-1, but not of E-selectin, on the surface of cultured endothelial cells, compared with static cultures. Moreover, Ohtsuka et al22 reported that exposure of endothelial cells to laminar shear stress (7 dynes/cm²) reduced surface expression of VCAM-1.
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Thus, the aims of the present study were the following: (1) to investigate whether surface expression of E-selectin and ICAM-1 were modified by different patterns of flow, i.e., laminar or turbulent flow; and (2) to evaluate the functional significance of changes in surface expression of adhesive molecules induced by flow, by investigating the dynamic interaction between cultured endothelial cells and circulating leukocytes under a controlled flow.

MATERIALS AND METHODS

Endothelial cell culture. Endothelial cells were obtained from human umbilical veins (HUVEC) by collagenase digestion according to the method of Jaffe et al. The cells were first plated in 55-cm² tissue culture plates (Falcon Labware Division, Becton Dickinson, Milan, Italy) precoated with 0.2% bovine gelatin. The growth medium consisted of Medium 199 (GIBCO, Grand Island, NY) supplemented with 10% newborn calf serum (GIBCO) and 1% human serum, 20 mmol/L N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES; Sigma Chemical, St. Louis, MO), 100 U/mL penicillin, 100 μg/mL streptomycin, 250 ng/mL fungizone, 2 mmol/L glutamine (GIBCO), 15 U/mL heparin (Parke-Davis, Milan, Italy), and 50 μg/mL endothelial cell growth factor. Cultures were grown at 37°C in 5% CO₂, 95% air. Confluent HUVEC were passaged with 0.025% trypsin-0.02% EDTA (GIBCO) and were routinely used between the first and fifth passage. Cultured cells were identified as endothelial by their cobblestone morphology and the presence of factor VIII antigen, using indirect immunofluorescence microscopy. For shear stress experiments HUVEC were plated on 145-cm² plastic dishes (Falcon) and used 1 day after attaining confluence in Medium 199 plus 5% newborn calf serum and 5% of human serum (test medium).

Shear exposure experiments. Confluent monolayers of HUVEC were exposed to laminar or turbulent flow in a cone-and-plate apparatus similar to that described in detail elsewhere. The apparatus was designed using as a plate a 145-cm² cell culture dish (13.6 cm outer diameter [OD]) coated by a confluent monolayer of HUVEC. Laminar flow over the cell surface was induced using a cone angle of 0.5°, whereas turbulent flow was generated by increasing the flow velocity and using a cone angle of 5°. The apparatus was designed to maintain constant temperature (37°C) and humidified air with 5% CO₂. The cone rotation speed giving a shear value of 8 dyne/cm² was calculated from previously reported experimental measurements and from theoretical analysis of fluid motion in the cone-plate geometry.

The presence of secondary flow driven by centrifugal forces was estimated using the parameter R*, as described in detail by Sdougos et al. When R* > 1 secondary flow becomes important, turbulent flow develops, whereas for R* = 0 the centrifugal forces are small and the radial flow velocity is almost equal to zero in any point of the plate. Because R* is a function of radial position on the plate, some radially degree of variation in shear stress levels is expected. During laminar flow experiments R* < 0.2, indicating a small contribution of centrifugal forces and shear stress on the plate surface ranged from 7.7 to 8.2 dyne/cm² passing from its center to the outer part of the plate. In turbulent flow conditions R* and shear stress increase with radial position. However, values of R* were greater than 2 for more than 94% of the plate surface. Surface average shear stress was 8.6 dyne/cm², whereas maximum shear stress at the edge of the cone was 11.7 dyne/cm². Three culture plates were used in each experiment. One plate was placed in the flow apparatus and the other two were kept in a normal incubator. Two different amounts of culture medium (22 and 80 mL) were used to completely fill the space between the plate and the cone, depending on the cone used. Cells maintained in static conditions were incubated with the same amount of medium as in the corresponding plate in the flow apparatus. One static culture was stimulated by incubation with recombinant human interleukin-1β (IL-1β, 10 U/mL; Boehringer Mannheim, Milan, Italy), and the other was treated with IL-1β (100 U/mL) 6 hours before the adhesion assay.

Adhesion assay under flow conditions. Before adhesion experiments a leukocyte suspension was prepared from fresh venous blood collected on EDTA (final concentration 5 mmol/L) and diluted with an equal volume of cold saline solution. The blood samples were centrifuged at 200g for 10 minutes at 4°C, the cell pellet was resuspended in 4 vol of Emagel (Behringwerke AG, Marburg, Germany) and erythrocytes were sedimented at 4°C for 40 minutes. Supernatant was removed, centrifuged at 500g for 7 minutes at 4°C, and the pellet washed twice by centrifugation with saline. Remaining erythrocytes were removed by ammonium chloride lysis at 4°C and centrifugation. After this procedure the cell viability, measured by trypan blue exclusion, was greater than 95%. Cells were then resuspended in culture medium at a final concentration of 10⁶ cells/mL.

Monolayers of untreated HUVEC or treated with IL-1β were then inserted in the flow chamber and placed on the stage of an inverted phase-contrast microscope with a thermostated hood (37°C). Cells exposed to flow were kept in the same flow chamber, used for flow...
exposure, that was transferred from the incubator to the microscope stage. In additional experiments, before the adhesion assay, monolayers of HUVEC pre-exposed to flow for 6 hours were incubated with mouse MoAb-adhesion blockade anti–ICAM-1 (BBIG-11, 10 µg/150 µL) for 20 minutes, or with a mouse isotype-matched MoAb (IgG1, clone 2H4; British Bio-Technology) as negative control. In each experiment leukocyte adhesion to unstimulated HUVEC or treated with IL-1β in static conditions or exposed to laminar flow was also evaluated.

Culture medium and cell suspension was pumped through the chamber, at controlled flow rates, using a syringe pump (Harvard Apparatus Inc, South Natick, MA). After initial perfusion of the chamber, at controlled flow rates, using a syringe pump (Harvard Apparatus Inc, South Natick, MA), leukocyte adhesion to unstimulated HUVEC or to 3.0 dynes/cm² to measure the number of cells rolling on the HUVEC surface. At this flow rate leukocytes rolling on the adhesion suspension that move much faster. Images of adhering leukocytes could be distinguished from their wake.

Images of adhering leukocytes on HUVEC surface were digitized and processed on a personal computer using general purpose image processing software (NIH Image, v. 1.43, Bethesda, MD). Adherent leukocytes were identified and counted at 2-minute intervals during the 10-minute perfusion at 1.5 dynes/cm² as previously described.39 The number of rolling cells on HUVEC surface at 3.0 dynes/cm² was determined on a series of 16 consecutive images digitized during a 10-second interval. All images were then superimposed by digital processing so moving cells could be distinguished from their wake.

Statistical analysis. Results are expressed as mean ± SE. Statistical analysis was performed using repeated measures ANOVA and the Tukey-Cicchetti test for multiple group comparisons, as appropriate. Data not uniformly distributed were analyzed by the Kruskal-Wallis test using Ryan’s procedure for specific comparisons. Statistical significance was defined as P < .05.

RESULTS

Endothelial expression of E-selectin and ICAM-1. Surface expression of E-selectin, as a percentage of fluorescent cells, is depicted in Fig 1 (A and B). The percentage of HUVEC labeled by E-selectin antibody in basal condition was very low, but IL-1β raised it considerably. The expression of E-selectin after exposure to either laminar or turbulent flow was the same as in static cultures (Fig 1, A and B). Figure 1 also shows mean fluorescence intensity of ICAM-1 in HUVEC exposed to static or flow conditions (C and D). As expected, IL-1β increased the expression of ICAM-1, as shown by the increase in mean fluorescence intensity (C and D). Exposure of HUVEC to laminar flow increased the mean fluorescence intensity of ICAM-1, compared with static controls, reflecting an upregulation of the corresponding molecule (C). When HUVEC were exposed to turbulent flow, mean fluorescence intensity was not modified (D).

Surface expression of E-selectin on HUVEC exposed to laminar or turbulent flow is shown in Fig 2. Neither laminar nor turbulent shear stress affected E-selectin expression on HUVEC for up to 15 hours. Thus, the percentage of fluorescent cells for E-selectin was comparable under laminar flow, turbulent flow, or static conditions at all observation times. However, IL-1β activation of HUVEC, in the static condition, significantly upregulated E-selectin expression (P < .01 vs resting HUVEC in static condition). The laminar-flow–induced increase in ICAM-1 expression is depicted in Fig 3. Mean fluorescence of ICAM-1, expressed as a percentage of stationary control, was not affected by 3-hour exposure of HUVEC to laminar flow (101% ± 3%). After 6-hour exposure to laminar flow ICAM-1 surface expression increased steeply (151% ± 13%, P < .01 vs static). ICAM-1 surface expression was still increased after a 15-hour exposure to flow (145% ± 12%, P < .01). In contrast, exposure of HUVEC to turbulent flow failed to significantly modify ICAM-1 expression at any interval considered (see Fig 3, 106% ± 5% at 6 hours, 101% ± 5% at 15 hours, not significant). As expected, incubation of HUVEC in static conditions with IL-1β, used as positive control for ICAM-1 induction, resulted in 173% ± 7%, 243% ± 30%, and 447% ± 59% expression in relation to unstimulated controls at 3, 6, and 15 hours of incubation, respectively.

Effect of supernatant of HUVEC exposed to flow on endothelial expression of ICAM-1. A second series of experiments was designed to establish whether ICAM-1 upregulation by laminar flow was caused by a direct effect of shear forces on HUVEC or was mediated by endothelial factors produced under flow conditions that could have induced the increase in surface expression of the adhesive molecule. HUVEC were incubated for 6 and 15 hours with supernatants of HUVEC exposed for the same interval to the static condition or laminar flow, then ICAM-1 expression was evaluated by FACS analysis. Surface expression of ICAM-1 on HUVEC incubated with supernatants conditioned under laminar flow or static conditions was comparable at both exposure times (Table 1).

Effect of shear stress on leukocyte adhesion to HUVEC. The adhesion of peripheral total leukocytes to control and IL-1β–treated HUVEC in static conditions or to HUVEC exposed to laminar flow for 6 hours at 8 dynes/cm² is presented in Figs 4 and 5. Images were digitized during the adhesion assay after 10 minutes of perfusion with leukocyte suspension (at 1.5 dynes/cm²). The dynamic interaction of leukocytes to HUVEC is depicted in Fig 5. As shown in panel A of Fig 4, a limited number of circulating cells adhered to control HUVEC during the 10-minute exposure, reaching a mean of 43 ± 16 adherent leukocytes/mm² after 10 minutes of perfusion. On IL-1β–activated HUVEC progressive leukocyte adhesion during perfusion was appreciably increased, compared with unstimulated cells (226 ± 72 adherent leukocytes/mm² after 10-minute perfusion, P < .05). Exposure of HUVEC to shear stress (8 dynes/cm² for 6 hours) markedly raised the number of adhering leukocytes during perfusion; on average 233 ± 67 leukocytes/mm² adhered on HUVEC surface after 10 minutes (P < .05 vs static HUVEC). The magnitude of the adhesive response induced by laminar flow was comparable to that observed with IL-1β incubation. The number of leukocytes rolling at 3 dynes/cm² is reported in Fig 5B. On unstimulated static HUVEC few rolling cells were detected (from 0 to 3 leukocytes/mm²). On HUVEC exposed to laminar flow the number of rolling cells slightly increased (on average 13 ± 5 leukocytes/mm²). However, on IL-1β–stimulated HUVEC the number of leukocytes rolling on the endothelial surface significantly in-
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**Fig 1.** Flow cytometric analysis of flow-induced changes in E-selectin and ICAM-1 expression. HUVEC exposed for 6 hours to laminar flow or static conditions were stained and analyzed by flow cytometer. HUVEC were incubated in static conditions with IL-1β 100 U/mL as positive control. Cells incubated with FITC-conjugated antibody alone were used as negative control (broken lines). Values shown in the figure indicate the percentage of fluorescent cells (A and B) for E-selectin, and mean fluorescence intensity (C and D) for ICAM-1.

Increased (averaging 51 ± 15 rolling leukocytes/mm²) compared with HUVEC maintained in the static condition and to HUVEC exposed to flow.

We also investigated whether flow-induced leukocyte adhesion was ICAM-1 dependent by treating HUVEC exposed to shear stress (8 dynes/cm² for 6 hours) with MoAb anti-ICAM-1. As shown in Fig 6A, the number of adherent leukocytes at the end of perfusion on HUVEC exposed to laminar flow was significantly increased compared with the respective static controls (174 ± 24 v 88 ± 11 leukocytes/mm², P < .05). Treatment with MoAb anti-ICAM-1 completely blocked flow-induced increase in leukocyte adhesion and the number of adherent leukocytes was comparable to static controls (73 ± 8 v 68 ± 21 leukocytes/mm², Fig 6B). Treatment with irrelevant MoAb did not significantly affect leukocyte adhesion on HUVEC exposed to laminar flow (161 ± 18 v 174 ± 24 leukocytes/mm²).

**DISCUSSION**

The present results show that percentage of fluorescent cells for endothelial E-selectin is not modified by flow conditions, whereas ICAM-1 expression greatly increases with

**Fig 2.** Effect of laminar (■) and turbulent flow (□) on E-selectin expression on endothelial cells. HUVEC were exposed for 3, 6, and 15 hours to laminar (8 dynes/cm²) or turbulent flow (1 to 12 dynes/cm²) or static conditions (■). As positive static control, HUVEC were stimulated with IL-1β (100 U/μL). Data are expressed as mean ± SE. *P < .01 versus static or flow condition. †P < .01 versus IL-1β-treated HUVEC at 3 and 6 hours.
time after exposure to laminar flow. Turbulent flow did not increase either E-selectin or ICAM-1 expression at any time considered. These findings extend previous observations that hemodynamic shear forces are major determinants of ICAM-1 expression on human endothelial cells. Our experiments also documented that supernatants of endothelial cells exposed to static or laminar flow conditions did not influence surface expression of ICAM-1 in HUVEC. This suggests that the laminar flow-induced increase in ICAM-1 expression is a direct effect of laminar flow on the endothelial ICAM-1 synthesis pathway rather than the consequence of stimulatory molecules released by the endothelium under flow conditions.

Little is known about the intracellular signals involved in triggering ICAM-1 expression in endothelial cells. Lane et al. suggested that protein kinase C (PKC) might be involved in IL-1, tumor necrosis factor (TNF), and lipopolysaccharide (LPS)-induced upregulation of ICAM-1 on endothelial cells. However, Myers et al. indicate that besides activation of PKC other regulatory pathways are probably involved in the IL-1- and LPS-induced increase in endothelial surface expression of ICAM-1. It has been suggested that activation of PKC mediates intracellular events that alter the endothelial cell genetic program in response to fluid shear stress. By increasing endothelial cell phosphoinositide turnover shear stress induces inositol trisphosphate and diacylglycerol second messenger activation that, in turn, promotes release of calcium from intracellular storage pools and eventually activates PKC. This last step activates transcription of endothelial genes for platelet derived growth factor and tissue plasminogen activator, both of which are modulated by flow conditions.

Resnick et al. showed that shear stress also has a direct

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**Table 1. Expression of ICAM-1 by Endothelial Cells Incubated With Supernatant of HUVEC Exposed to Laminar Flow or Static Conditions**

<table>
<thead>
<tr>
<th>Exposure Time</th>
<th>Mean Fluorescence Intensity</th>
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<tbody>
<tr>
<td></td>
<td>6 h</td>
</tr>
<tr>
<td>Laminar flow</td>
<td>246 ± 7</td>
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<tr>
<td>Static</td>
<td>286 ± 41</td>
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Data are the mean ± SE of three separate experiments.
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Impact on gene transcription in cultured endothelial cells. They identified a cis-acting element for PDGF-B gene required for shear-stress responsiveness, defined as shear-stress responsive element (SSRE). A core-binding sequence (GAGACC) of SSRE is present within the 5' promoter region of several unrelated genes such as tissue plasminogen activator, transforming growth factor β, and ICAM-1, all of which respond to shear stress in vascular endothelium. However, E-selectin and VCAM-1 are not upregulated by shear stress and do not contain the SSRE in their promoters. In the present study, laminar flow, but not turbulent shear stress, increased ICAM-1 expression. It is tempting to speculate that in endothelial cells turbulent flow might not activate the SSRE-core-binding sequence in the promoter of ICAM-1 gene.

Flow-related shear stress alters endothelial cell structure to the point that it causes major changes in cell shape. Thus, laminar but not turbulent shear stress induces cell alignment in the direction of flow. In vivo and in vitro evidence indicates that laminar shear stress influences the F-actin organization in the cytoskeleton. A recent study has shown a direct association of actin-containing cytoskeleton with ICAM-1; this interaction leads to a specialized cell-surface distribution of ICAM-1 both on an adherent kidney epithelial cell line (COS cell) and in transformed B cells. The same study provided evidence that actinin, an actin-binding cytosolic protein, associates with the intracytoplasmic domain of ICAM-1 and codistributes with ICAM-1 in cells, suggesting that it may serve as an anchorage between ICAM-1 and the actin-containing microfilament network. It is possible that the increased expression of ICAM-1 observed after HUVEC exposure to laminar, but not to turbulent flow, is caused by a different regulation of cytoskeletal organization in response to the two types of shear stress.

Our finding that flow upregulates endothelial ICAM-1 expression was associated with significant increase of leukocyte adhesion to HUVEC pre-exposed to flow. In addition,
functional blocking of ICAM-1 on endothelial cells pre-exposed to flow abolished the upregulated leukocyte adhesion. All these evidences indicate that laminar flow directly and selectively regulates de novo synthesis of ICAM-1, which promotes the leukocyte-endothelium interaction. Of interest, the adhesive response elicited by flow was comparable to that of IL-1β, one of the most potent inducers of endothelial cell adhesive properties. At variance to adhesion, leukocyte rolling induced by exposing HUVEC to fluid shear stress was markedly lower than that induced on IL-1β-activated HUVEC. This is in line with our FACS analysis data that laminar flow did not increase surface expression of E-selectin, the key molecule that supports leukocyte rolling. Despite the lower number of rolling leukocytes, the adhesion of circulating cells was comparable on flow-conditioned HUVEC and on IL-1β-treated cells.

Numerous studies have reported the expression of adhesion molecules by endothelial cells in vitro. These studies have always used endothelial cells cultured under static conditions. Our results show that endothelial cells exposed to laminar flow, as in the physiologic state, markedly adjust their adhesion molecule pattern. Thus, in vitro studies designed to clarify the mechanisms that govern surface expression of adhesion molecules by endothelial cells can no longer neglect adaptation effects induced by flow in these cells. In addition, the present study may offer a novel possible interpretation to the different pathway, mentioned previously, of leukocyte adhesion to the endothelium in vivo and in vitro. One can speculate that in vivo endothelial cells exposed to flow of blood adapt ICAM-1 expression to allow circulating cells to adhere at vascular wall at higher shear stresses than observed in vitro. On the other hand, a possible implication of the present data in the context of pathophysiologic of the circulation is that in regions of low shear, where the contact of circulating cells with the vascular wall is favored, downregulation of ICAM-1 could serve to limit leukocyte-endothelial interaction. More complex shear stress pathways, like disturbed or turbulent flows, seem to have a different impact on ICAM-1 expression.

In conclusion, our results indicate that laminar flow selectively upregulates the surface expression of endothelial cell adhesion molecule ICAM-1 and directly modulates the adhesion of leukocytes. Thus, local blood flow conditions appear to be important in leukocyte-endothelial interaction and extravasation.

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