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Influence of Lidocaine on Endotoxin-induced Leukocyte-Endothelial Cell Adhesion and Macromolecular Leakage in Vivo

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Background: Endotoxin activates leukocyte-endothelial cell adhesion, vascular leakage, and changes in vascular microhemodynamics. The aim of this study was to determine whether lidocaine, which inhibits the activation of leukocytes, could attenuate microcirculatory disturbances during endotoxemia.

Methods: Thirty anesthetized male rats were randomly assigned to receive one of three treatments ($n = 10$ for each group): infusion of saline (control group), infusion of *Escherichia coli* endotoxin (LPS group: $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ lipopolysaccharides) without lidocaine treatment, or infusion of endotoxin with lidocaine pretreatment 30 min before baseline measurements (lidocaine group: intravenous bolus of 2 mg/kg and continuous infusion of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Leukocyte adherence, erythrocyte velocity (V_{RBC}), and vessel diameters (D_v) were determined at baseline and at 60 and 120 min in mesenteric postcapillary venules using *in vivo* videomicroscopy. Macromolecular leakage was determined by measuring the extravasation of fluorescence-labeled albumin. Venular wall shear rate (τ) was calculated according to the equation $\tau = 8 \cdot V_{\text{RBC}} \cdot D_v^{-1}$.

Results: Lidocaine significantly attenuated the increase of leukocyte adherence during endotoxemia. There were no significant differences of τ within or between the groups. Macromolecular leakage exhibited the greatest increase in the LPS group. In the lidocaine group, it was significantly decreased but still increased compared with the control group.

Conclusions: These results show that lidocaine attenuates endotoxin-induced alterations in leukocyte-endothelial cell adhesion and macromolecular leakage, which suggests that

lidocaine may have a therapeutic role in preventing endothelial damage in sepsis. (Key words: Anesthetics, local: lidocaine. Endotoxemia. Intestinum: endothelium; leukocyte adherence; mesentery plasma extravasation. Measurement techniques: *in vivo* videomicroscopy.)

LEUKOCYTE-ENDOTHELIAL interactions play a pivotal role in the development of endotoxin-induced organ dysfunction.^{1,2} Adherence of activated leukocytes to the endothelium represents a crucial step in the process of neutrophil-mediated endothelial damage. This is characterized by increased emigration of leukocytes, accumulation of leukocytes in the tissues, and increased vascular permeability.^{3,4} In a shock model, investigators showed that surviving animals have significantly lower fractions of activated leukocytes with a reduced adhesiveness.⁵ Further, mice deficient in the intercellular adhesion molecule-1 were more resistant to the lethal effects of high doses of endotoxin. This is correlated with a decrease in neutrophil infiltration in the liver.⁶ Therefore, diminishing leukocyte adhesion may be a therapeutic approach to attenuating sepsis-induced organ injury.

Lidocaine has various inhibitory effects on neutrophil function. It reduces leukocyte adhesion to the microvascular endothelium⁷ and to nonbiologic surfaces.⁸ It also inhibits the migration of leukocytes into the inflammatory site.^{9,10} In addition, research has shown that lidocaine attenuates leukocyte production of prostaglandins,¹¹ leukotrienes,¹² and thromboxanes.¹⁰ Lidocaine also reduces free radical production by neutrophils¹³ and inhibits superoxide anion release.^{14,15} Further, it decreases the release of protease from neutrophils and macrophages by stabilizing their cell membranes.¹⁶

The aim of this study was to determine whether lidocaine pretreatment can attenuate leukocyte adherence and vascular leakage during endotoxemia. To visualize leukocyte-endothelial interactions and plasma extravasation, we chose *in vivo* microscopy of rat mesentery.

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Materials and Methods

Animal Preparation

All experimental procedures and protocols used in this investigation were reviewed and approved by the Governmental Animal Protection Committee. Experiments were performed on male Wistar rats (weighing 250–350 g). Anesthesia was induced using pentobarbital (60 mg/kg) injected intraperitoneally (Nembutal; Sanofi, Hannover, Germany). A tracheostomy was performed to facilitate spontaneous ventilation. Blood pressure was monitored using a pressure transducer (Hellige Servomed, Freiburg, Germany) connected to a cannula in the left carotid artery. Intravenous drugs were administered *via* a right jugular vein cannula. Rectal temperature was measured with a thermistor probe and maintained at 37°C using a heating lamp. The abdomen was opened through a midline incision, and the ileal portion of the mesentery was spread carefully over a plastic stage beneath the intravital microscope. The preparation was superfused continuously with a thermostat-controlled (36°C), bicarbonate-buffered salt solution (132 mM sodium chloride, 4.7 mM potassium chloride, 2 mM calcium chloride, 1.2 mM magnesium chloride, and 18 mM sodium bicarbonate) equilibrated with 5% carbon dioxide in nitrogen to adjust the pH to 7.35.

Experimental Protocol

Rats were randomized into 3 groups of 10 animals each. After a 30-min stabilization period and exteriorization of the mesentery, animals in the lidocaine group received an intravenous bolus of 2 mg/kg b.w. lidocaine (Xylocain; Astra Chemicals, Wedel, Germany) followed by a continuous infusion of 2 mg · kg⁻¹ · h⁻¹. Animals in the LPS and the control groups were given equivalent amounts of 0.9% NaCl. In the lidocaine and LPS groups, endotoxemia was induced 60 min after exteriorization of the mesentery by continuous intravenous infusion of 2 mg · kg⁻¹ · h⁻¹ endotoxin (lipopolysaccharide from *Escherichia coli* 026:B6; Sigma Chemical Co., Deisenhofen, Germany) diluted in 0.9% NaCl. Animals in the control group received a volume-equivalent continuous intravenous infusion of 0.9% NaCl.

Intravital Microscopy

The mesenteric microcirculation was observed using a custom-designed microscope (Orthoplan; Leica, Wetzlar, Germany) equipped with a ×40 objective (Achromplan 40/0.75W; Zeiss, Jena, Germany). The exteriorized mesentery was visualized either by transillumina-

tion (150 W cold light fountain; KL 1500 electronic, Schott, Wiesbaden, Germany) or by epi-illumination using an epifluorescence illuminator (Ploemopak; Leica) consisting of a 100 W short arc mercury lamp (Osram, Munich, Germany) and a filter system for the fluorescence excitation (green light excitation: N 2.1; blue light excitation: I 3; Leica). To protect the preparation from heat, a heat protection filter (KG1; Leica) was located in the body of the microscope. Microscopic images were transferred to a monitor (PVM 1444QM; Sony Corp., Tokyo, Japan) by a low-light camera (Kappa CF 8/1; Kappa Messtechnik, Gleichen, Germany) and recorded on videotape using a video recorder (Panasonic S-VHS AG-7350-E; Matsushita, Japan).

Measurement of Erythrocyte Velocity

Mean erythrocyte velocities (V_{RBC}) and vessel diameters (D_v) of single unbranched postcapillary venules (25–40 μ m diameter) were analyzed off-line at baseline (0 min) and at 60 and 120 min after the beginning of continuous endotoxin or saline infusion, using a computer-assisted video analysis system (Cap Image; Zeintl, Heidelberg, Germany). Therefore, fluorescence-labeled erythrocytes from donor rats were injected before intravital microscopy (0.5 ml/kg b.w.; hematocrit 50%). These erythrocytes were labeled with a red fluorescent cell linker kit (PKH26-GI; Sigma Chemical Co.) using a modified procedure of Horan *et al.*¹⁷ By analyzing the video recordings, the frame-to-frame method was used to determine the velocity of the fluorescence-labeled erythrocytes. Mean blood cell velocity in the venule was calculated by averaging the velocities of at least 20 single erythrocytes. The velocity of faster erythrocytes in the center of the vessel and of slower erythrocytes near the vascular wall was evaluated according to the frequency of their appearance. Venular wall shear rate (τ) was calculated based on the newtonian definition $\tau = 8 (V_{RBC}/D_v)$.¹⁸

Leukocyte-Endothelial Interactions

The behavior of leukocytes was visualized using transillumination microscopy at 0, 60, and 120 min. In the venules of the exteriorized rat mesentery, adherent leukocytes can be observed without staining. The mesentery of the rat is thin and provides clear visualization of the vessel wall and blood cellular elements. Adherent leukocytes were determined off-line during playback of the videotaped images and were defined as cells that remain stationary on the endothelial wall for at least 30

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s. Leukocyte adherence was expressed as the number of cells per 100 μm of venule length.

Measurement of Macromolecular Leakage

To quantify albumin leakage across mesenteric venules, 50 mg/kg fluorescein isothiocyanate-labeled bovine albumin (Sigma Chemical Co.) was injected intravenously 15 min before each experiment.¹⁹ The recorded fluorescent images were digitalized. The gray levels, depending on the fluorescence intensity (gray levels range from 0 [black] to 255 [white]), were measured within three segments of the venule (I_v) and in three contiguous areas of the perivenular interstitium (I_p). Macromolecular leakage was determined as the ratio $I_p:I_v$ at 0, 60, and 120 min.

Monitoring

Mean arterial blood pressure and heart rate were recorded at baseline and at 60 and 120 min. The hematocrit concentration and systemic leukocyte and systemic platelet counts were determined at baseline and after 60 and 120 min using a hematology analyzer system that was calibrated for rat blood cells (CP 9000-3; Serono-Baker-Diagnostics, Allentown, PA).

Statistical Analysis

All data are expressed as mean \pm SD. For statistical analysis, a two-way analysis of variance for repeated measurements followed by the Scheffé test was used. Differences resulting in P values < 0.01 were considered significant.

Results

Macrobemodynamic Changes

At baseline, all animals showed no statistical differences in mean arterial blood pressure. After 120 min of endotoxemia, mean arterial blood pressure remained unchanged in the lidocaine group and in the control group, whereas it was decreased in the LPS group (table 1).

The baseline values for heart rate did not differ among the groups. Although there was a tendency to increasing heart rate in all groups, this increase was not significant.

Microhemodynamic Changes

In all three groups, venular diameters (D_v) remained unchanged and showed no differences among them (table 1).

Erythrocyte velocity (V_{RBC}) at baseline was similar in all three groups. In endotoxin-treated animals (the LPS and lidocaine groups), V_{RBC} decreased significantly after 120 min. In the control group, V_{RBC} remained unchanged during the entire observation period.

Leukocyte Adherence

Figure 1 shows the results of leukocyte adherence. Before the administration of endotoxin, there was no significant difference in the number of adherent leukocytes between the groups. Baseline levels of leukocyte adherence were 3.6 ± 1.1 cells per 100/ μm venule length in the control group, 4.4 ± 1.1 cells per 100 μm in the LPS group, and 4.6 ± 0.7 cells per 100 μm in the lidocaine group. The number of adherent leukocytes increased significantly in the LPS group to 13.9 ± 3.4 cells per 100 μm at 120 min. Pretreatment with lidocaine attenuated the endotoxin-induced increase in leukocyte adherence. The number of adherent leukocytes increased in the lidocaine group only to 7.3 ± 0.4 cells per 100 μm . In the control group, the number of adherent cells remained nearly stable (5.3 ± 0.9 cells per 100 μm after 120 min).

Venular Wall Shear Rate

The mean values of venular wall shear rate decreased in all three groups but also showed high standard deviations. The decrease in all three groups was not significant (fig. 2).

Macromolecular Leakage

Figure 3 shows changes in macromolecular leakage. At baseline, the ratio $I_p:I_v$ did not differ among the groups (control group, 0.28 ± 0.02 ; LPS group, 0.27 ± 0.04 ; and lidocaine group, 0.27 ± 0.04). In all three groups, the $I_p:I_v$ ratio increased significantly during the 120-min observation period (after 120 min: control group, 0.38 ± 0.06 ; LPS group, 0.58 ± 0.09 ; and lidocaine group, 0.42 ± 0.09). However, the increase was significantly lower in the control group and in the lidocaine group compared with the LPS group after 120 min.

Changes in Systemic Blood Cell Counts

Table 2 shows changes in systemic blood cell counts. The hematocrit concentration remained unaltered throughout the experiment in all groups. In control animals, the leukocyte counts were not changed significantly. In the LPS group, the continuous infusion of endotoxin markedly reduced leukocyte counts after 60

Table 1. Macrohemodynamic and Microhemodynamic Changes in the Three Groups

		Time from Start of Endotoxin or Saline		
		0 min	60 min	120 min
MAP (mmHg)	Control	130 ± 7	134 ± 10	133 ± 7
	LPS	134 ± 6	132 ± 9	121 ± 13*†
	Lidocaine	124 ± 10	123 ± 11*	123 ± 13
HR (beats/min)	Control	363 ± 26	384 ± 37	396 ± 34
	LPS	366 ± 42	399 ± 25	421 ± 49
	Lidocaine	353 ± 30	381 ± 25	408 ± 25
D _v (μm)	Control	32.3 ± 2.3	32.2 ± 2.3	32.2 ± 2.4
	LPS	30.8 ± 3.0	30.7 ± 2.4	30.9 ± 2.2
	Lidocaine	31.6 ± 3.9	31.7 ± 3.7	31.7 ± 3.7
V _{RBC} (mm/sec)	Control	1.8 ± 0.5	1.5 ± 0.4	1.5 ± 0.6
	LPS	2.0 ± 0.7	1.7 ± 0.7	1.1 ± 0.7†
	Lidocaine	2.0 ± 0.4	1.6 ± 0.5	1.3 ± 0.5†

Values are mean ± SD.

MAP = mean arterial pressure; HR = heart rate; RR = respiratory rate; D_v = venular diameter; V_{RBC} = erythrocyte velocity.

* *P* < 0.01 versus control group.

† *P* < 0.01 versus 0 min.

min. Pretreatment with lidocaine prevented this decrease at 60 min but not at 120 min of endotoxemia.

Systemic platelet counts remained stable in the control group during the observation period. In both endo-

toxin-treated groups it showed a significant decrease after just 60 min of endotoxemia. However, only the LPS group had significantly lower platelet counts compared with the control group after 120 min.

Discussion

Leukocyte-endothelial cell interactions play an important role in the pathogenesis of sepsis and sepsis-

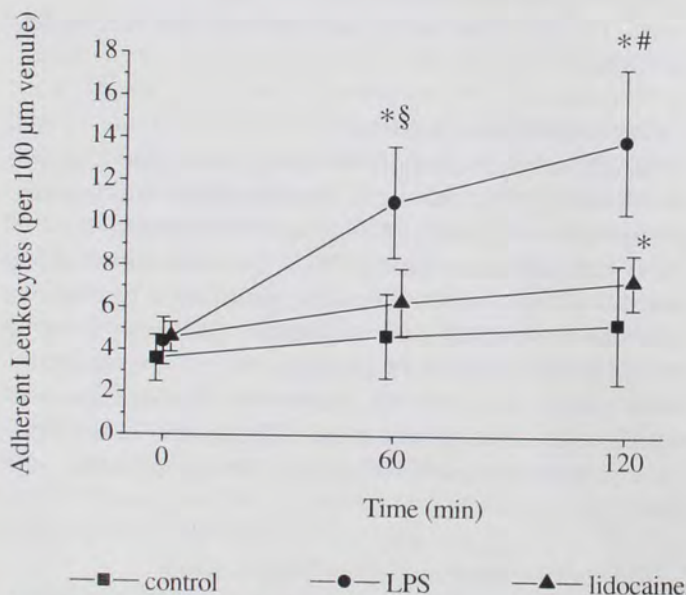


Fig. 1. Effects of LPS infusion on the number of adherent leukocytes in postcapillary venules of rat mesentery with (lidocaine group, *n* = 10) and without (LPS group, *n* = 10) lidocaine pretreatment. Animals in the control group (*n* = 10) had no LPS or lidocaine pretreatment. Data are mean ± SD. **P* < 0.01 versus 0 min; #*P* < 0.01 versus the control group and lidocaine group; §*P* < 0.01 versus the control group.

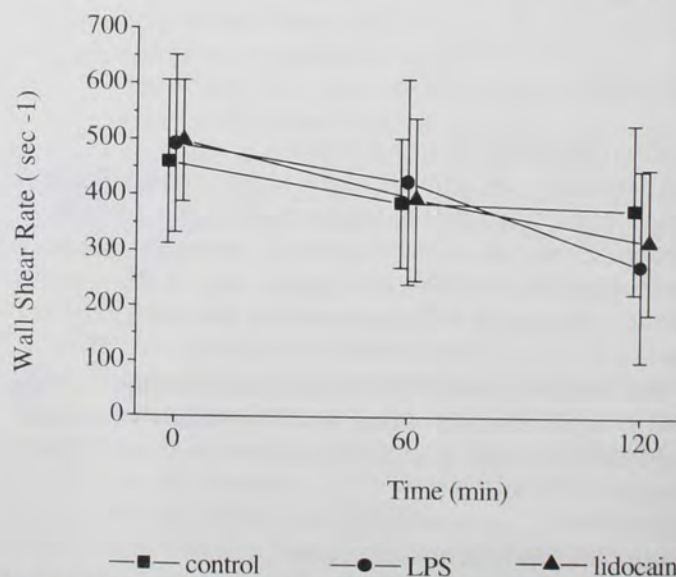


Fig. 2. Wall shear rate of all three groups during the observation period. There were no significant changes within or among the groups. Data are mean ± SD.

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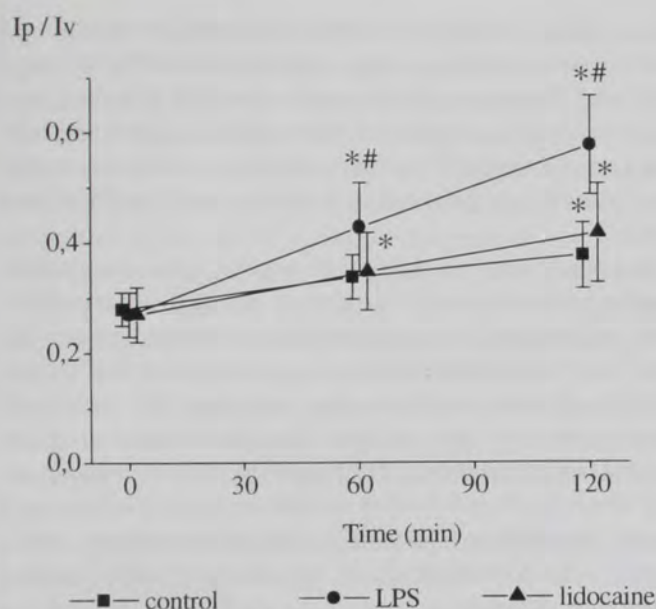


Fig. 3. Fluorescein isothiocyanate-labeled albumin extravasation expressed as a ratio of perivenular fluorescence intensity (I_p) to venular fluorescence intensity (I_v). Data are mean \pm SD. * $P < 0.01$ versus 0 min; # $P < 0.01$ versus the control group and lidocaine group.

related multiple-organ dysfunction syndrome.¹⁻³ Damage of the microvascular integrity, with an increase in permeability, is mediated in part by the recruitment and adhesion of neutrophils to the endothelium and by their release of destructive molecules.^{1,20} Pulmonary vascular permeability during endotoxemia, for example, is increased by activated leukocytes that accumulate in the

lung.²¹ The modulation of leukocyte-endothelial cell interactions thus may be a therapeutic tool in attempts to control the course of sepsis and development of multiple-organ system failure.²²

The plasma concentration of lidocaine in the range of 3-5 $\mu\text{g}/\text{ml}$ is considered the therapeutic concentration for an antiarrhythmic effect.²³ In peridural anesthesia, a mean peak plasma concentration of 3.26-4.11 $\mu\text{g}/\text{ml}$ lidocaine was measured 10 min after applying 10 ml 2% lidocaine.²⁴ After obturator nerve block combined with spinal anesthesia in patients undergoing transurethral resection procedures, plasma concentrations of lidocaine were not higher than 5.1 $\mu\text{g}/\text{ml}$.²⁵ Supradist *et al.*²⁶ determined lidocaine kinetics in the rat and found the highest peak blood lidocaine levels of 3.16 ± 0.56 $\mu\text{g}/\text{ml}$ 5 min after an intravenous bolus of 2.5 mg/kg lidocaine. In our study, we used the same dosage of lidocaine that Takao *et al.*²⁷ used in their rabbit model. They measured plasma lidocaine concentrations between 1.4-2.5 $\mu\text{g}/\text{ml}$. At this concentration, lidocaine had a prophylactic effect on initial hyperoxic lung injury. These results suggest that the dosage used in the present study produced plasma concentrations in a clinically relevant range and that it was unlikely to achieve plasma levels beyond 10 $\mu\text{g}/\text{ml}$, which is considered to be the toxic threshold for lidocaine.

In another study, lidocaine infusion at a rate of 0.6 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ reduced albumin extravasation in burn injuries in rats.²⁸ In patients with coronary heart disease, serum lidocaine concentrations between 1.0-5.6 $\mu\text{g}/\text{ml}$ caused a significantly lower release of O_2^- by neutro-

Table 2. Changes in Hematocrit, Peripheral White Blood Cell, and Platelet Counts in the Three Groups

		Time from Start of Endotoxin or Saline		
		0 min	60 min	120 min
Hct (%)	Control	44 \pm 3	43 \pm 3	43 \pm 4
	LPS	45 \pm 4	47 \pm 5	44 \pm 7
	Lidocaine	45 \pm 4	46 \pm 7	42 \pm 6
WBC ($\times 10^3/\text{mm}^3$)	Control	7.3 \pm 1.9	7.8 \pm 2.3	8.5 \pm 2.9
	LPS	8.0 \pm 1.5	5.6 \pm 1.3*†	3.7 \pm 1.0*†
	Lidocaine	6.9 \pm 1.2	6.6 \pm 1.4†	4.7 \pm 1.3*†
PLT ($\times 10^3/\text{mm}^3$)	Control	782 \pm 128	718 \pm 156	627 \pm 161
	LPS	816 \pm 154	552 \pm 163*†	368 \pm 153*†
	Lidocaine	792 \pm 176	628 \pm 107*	516 \pm 139*

Values are mean \pm SD.

Hct = hematocrit; WBC = white blood cells; PLT = platelets; LPS = lipopolysaccharide.

* $P < 0.01$ versus 0 min.

† $P < 0.01$ versus control group.

phils compared with the release in healthy persons.¹⁵ Our study shows that endotoxemia induces a progressive increase in leukocyte adherence. However, there was no significant decrease in venular wall shear rate. Other investigators found a reduction in venular shear rate in similar experiments but could show that this reduction in venular wall shear rate alone was not responsible for most of the adherent leukocytes.^{4,29} Leukocyte adherence to the vascular endothelial surface is mediated by several mechanisms. These include the expression of adhesion molecules such as the leukocyte glycoprotein adhesion complex CD11/CD18 on the surface of activated leukocytes and the generation of intercellular adhesion molecule-1 on endothelial cells. The reduction of microhemodynamic dispersal forces helps leukocytes to attach to the endothelium.³⁰

In our study, administration of lidocaine before the endotoxin challenge attenuated leukocyte adherence. This was not caused by differences in venular wall shear rate. Although erythrocyte velocity decreased in the endotoxin-treated groups after 120 min and venular diameter remained stable, venular shear rate did not change significantly. There are several mechanisms by which lidocaine can prevent shear force-independent leukocyte adhesion to the venular endothelium. First, lidocaine attenuates leukocyte activation³¹ and inhibits the migration of leukocytes into the inflammatory site.⁸⁻¹⁰ Neutrophil function, including free radical production, is reduced.¹⁵ Oxygen radicals play a key role in activating leukocytes and endothelial cells and in promoting leukocyte adherence. Several intravital microscopy studies showed that oxygen radical scavengers can prevent firm leukocyte attachment to the endothelium.^{32,33} It appears unlikely that lidocaine itself possesses free radical scavenging properties, but it prevents further free radical generation by inhibiting the activation of leukocytes.¹⁵ Recently investigators found that pretreatment with lidocaine significantly attenuates endotoxin-induced acute lung injury in rabbits³⁴ by attenuating the accumulation and the O₂⁻ production of neutrophils. The mechanism is still uncertain but may be related to an alteration in biomembrane function. Lidocaine electrically stabilizes biomembranes and blocks sodium channels, thereby inhibiting depolarization by reducing sodium and potassium exchange.^{35,36} This accounts for the antiarrhythmic effect of lidocaine. Similar events are believed to be involved in enzyme and superoxide anion release during stimulation of neutrophils.³⁷

Another endogenous modulator of leukocyte adhesion is nitric oxide. Research has shown that nitric ox-

ide-synthase inhibitors increase the number of adherent leukocytes attached to the endothelium of mesenteric vessels.³⁸ Nitric oxide has been reported to have a protective function in attenuating tissue injury during endotoxemia or sepsis.³⁹ Lidocaine has been shown to stimulate nitric oxide generation in human peripheral neutrophils.⁴⁰

Pentobarbital in a dose of 60 mg/kg given intraperitoneally was necessary to achieve surgical anesthesia in our preparation. Although we did not verify the responsive of the microvasculature to changes in the sympathetic efferent outflow after applying this relatively large dose, we can assume that the response of the vessel remained intact. Pentobarbital used in a comparable dose has been shown to maintain the diameters of small third-order arterioles in the rat cremaster muscle within the normal range of values observed in unanesthetized, decerebrated rats.⁴¹

In our study, endotoxemia increased macromolecular leakage. Pretreatment with lidocaine significantly attenuated the endotoxin-induced increase in microvascular permeability. This result is confirmed by previous studies showing that local anesthetics are potent inhibitors of plasma extravasation after peritonitis⁴² and burn trauma.²⁸ Mikawa *et al.*³⁴ showed in a pretreatment-model that lidocaine reduces the extravasation of albumin in the lungs of endotoxic rabbits. This effect of lidocaine was also demonstrated by Stelzner *et al.*¹⁴ Kurose *et al.*²⁹ suggested a close correlation among leukocyte adherence, the formation of oxygen radicals by adherent leukocytes, and the development of increased permeability in postcapillary venules during endotoxemia. Similarly, Yi and Ulich⁴³ reported that the microvascular leak in postcapillary venules caused by endotoxin was dependent on the accumulation of neutrophils. Thus the prevention of hyperpermeability by lidocaine in our experiments may be due to the reduced leukocyte adherence. Other reasons for increased plasma extravasation include the activation of complement system¹ and the release of histamine.⁴⁴ Complement activation is partly induced by adherent leukocytes. Thus the attenuating effect of lidocaine on leukocyte adherence could also attenuate the activation of the complement system. Furthermore, histamine induces protein leakage independent of leukocyte adherence.⁴⁵ The release of histamine from mast cells may be reduced by the membrane-stabilizing effects of lidocaine.¹⁶

In our study, mean arterial blood pressure only decreased in the LPS group during endotoxemia. This result supports the view that lidocaine can attenuate the

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severity of hypotension caused by endotoxemia. Taniguchi *et al.*⁴⁶ described a similar result.

Increased leukocyte adherence during endotoxemia was associated with low circulating leukocyte counts. This finding corresponds with the results obtained by Barroso-Aranda *et al.*,⁵ who described rapid onset of neutropenia after injection of endotoxin in rats. In our study, pretreatment with lidocaine did not significantly attenuate the decrease in systemic leukocyte count during endotoxemia, although leukocyte adherence in the postcapillary venules was much lower in the lidocaine group. This decrease in the systemic white blood cell count in the lidocaine group suggests that leukocyte accumulation occurs in tissues other than the mesentery.

The systemic platelet count decreased during endotoxemia, indicating a high consumption or destruction of platelets. This decrease could be attenuated by lidocaine pretreatment. Platelets aggregate with activated leukocytes during endotoxemia. Thus the attenuated decrease in the platelet count in the lidocaine group may be a secondary effect of a reduced leukocyte activation. However, lidocaine may also have a direct platelet preservation effect.

A potentially negative aspect of the inhibitory effect of lidocaine on neutrophil activation is the possible increase in susceptibility to infection. Peck *et al.*¹⁵ showed that the microbicidal function of neutrophils from patients receiving lidocaine infusions was only slightly decreased. This suggests that there is sufficient remaining neutrophil function to minimize the risk of a higher susceptibility to infection.

In conclusion, our results show that lidocaine attenuates leukocyte activation and adherence to vascular walls during endotoxemia and preserves endothelial integrity. Furthermore, lidocaine maintained the mean arterial blood pressure. Although we used a pretreatment model, these results suggest that lidocaine may be a useful drug for reducing inflammation and preventing endothelial damage in sepsis.

References

1. Bone RC: Inhibitors of complement and neutrophils: a critical evaluation of their role in the treatment of sepsis. *Crit Care Med* 1992; 20:891-8
2. Redl H, Nikolai A, Kneidinger R, Schlag G: Endothelial and leukocyte activation in experimental polytrauma and sepsis. *Behring Inst Mitt* 1993; 92:218-28
3. Williams JH Jr, Patel SK, Hatakeyama D, Arian R, Guo K, Hickey TJ, Liao SY, Ulich TR: Activated pulmonary vascular neutrophils as early mediators of endotoxin-induced lung inflammation. *Am J Respir Cell Mol Biol* 1993; 8:134-44
4. Harris NR, Russell JM, Granger DN: Mediators of endotoxin-induced leukocyte adhesion in mesenteric postcapillary venules. *Circ Shock* 1994; 43:155-60
5. Barroso Aranda J, Zweifach BW, Mathison JC, Schmid-Schönbein: Neutrophil activation, tumor necrosis factor, and survival after endotoxic and hemorrhagic shock. *J Cardiovasc Pharmacol* 1995; 25:23-9
6. Xu H, Gonzalo JA, St Pierre Y, Williams IR, Kupper TS, Cotran RS, Springer TA, Gutierrez-Ramos JC: Leukocytosis and resistance to septic shock in intercellular adhesion molecule 1-deficient mice. *J Exp Med* 1994; 180:95-109
7. Giddon DB, Lindhe J: In vivo quantitation of local anesthetic suppression of leukocyte adherence. *Am J Pathol* 1972; 68:327-38
8. Hammer R, Dahlgren C, Stendahl O: Inhibition of human leukocyte metabolism and random mobility by local anaesthesia. *Acta Anaesthesiol Scand* 1985; 29:520-3
9. MacGregor RR, Thorner RE, Wright DM: Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood* 1980; 56:203-9
10. Schreiner A, Hopen G: Adhesion and locomotion of human leukocytes in vitro; importance of protein coating; effect of lidocaine, ethanol and endotoxin. *Acta Pathol Microbiol Scand* 1979; 87:333-40
11. Goel RK, Tavares IA, Nellgard P, Jönsson A, Cassuto J, Bennett A: Effect of lignocaine on eicosanoid synthesis by pieces of human gastric mucosa. *J Pharm Pharmacol* 1994; 46:319-20
12. Sinclair R, Eriksson AS, Gretzer C, Cassuto J, Thomsen P: Inhibitory effects of amide local anesthetics on stimulus-induced human leukocyte metabolic activation, LTB₄ release and IL-1 secretion in vitro. *Acta Anaesthesiol Scand* 1993; 37:159-65
13. Siminiak T, Wysocki H, Veit A, Maurer HR: The effect of selected antiarrhythmic drugs on neutrophil free oxygen radicals production measured by chemiluminescence. *Basic Res Cardiol* 1991; 86:355-62
14. Stelzner TJ, Welsh CH, Berger E, McCullough RG: Antiarrhythmic agents diminish thiourea-induced pulmonary vascular protein leak in rats. *J Appl Physiol* 1987; 63:1877-83
15. Peck SL, Johnston RB Jr, Horwitz LD: Reduced neutrophil superoxide anion release after prolonged infusions of lidocaine. *J Pharmacol Exp Ther* 1985; 235:418-22
16. Wachtfagel YT, Kucich U, Greenplate J, Gluszko P, Abrams W, Weinbaum G, Wenger RK, Rucinski B, Niewiarowski S, Edmunds LH, Colman RW: Human neutrophil degranulation during extracorporeal circulation. *Blood* 1987; 69:324-30
17. Horan PK, Melnicoff MJ, Jensen BD, Slezak SE: Fluorescent cell labeling for in vivo and in vitro cell tracking. *Meth Cell Biol* 1990; 33:469-90
18. House SD, Lipowsky HH: Leukocyte-endothelium adherence: microhemodynamics in mesentery of the cat. *Microvasc Res* 1987; 34:363-79
19. Kurose I, Anderson DC, Miyasaka M, Tamatani T, Paulson JC, Todd RF, Rusche JR, Granger DN: Molecular determinants of reperfusion-induced leukocyte adhesion and vascular protein leakage. *Circ Res* 1994; 74:336-43
20. Weiss SJ: Tissue destruction by neutrophils. *N Engl J Med* 1989; 320:365-76
21. Uchiba M, Okajima K, Murakami K, Okabe H, Takatsuki K:

- Endotoxin-induced pulmonary vascular injury is mainly mediated by activated neutrophils in rats. *Thromb Res* 1995; 78:117-25
22. Fujishima S, Aikawa N: Neutrophil-mediated tissue injury and its modulation. *Intensive Care Med* 1995; 21:277-85
 23. Collinsworth KA, Kalman SM, Harrison DC: The clinical pharmacology of lidocaine as an antiarrhythmic drug. *Circulation* 1974; 50:1217-30
 24. Mayumi T, Dohi, S, Takahashi T: Plasma concentrations of lignocaine associated with cervical, thoracic, and lumbar epidural anesthesia. *Anesthesia and Analgesia* 1983; 62:578-80
 25. Fujita Y, Kimura K, Furukawa Y, Takaori M: Plasma concentrations of lignocaine after obturator nerve block combined with spinal anaesthesia in patients undergoing transurethral resection procedures. *Br J Anaesth* 1992; 68: 596-8
 26. Supradist S, Notarianni LJ, Bennett PN: Lignocaine kinetics in the rat. *J Pharm Pharmacol* 1984; 36: 240-3
 27. Takao Y, Mikawa K, Nishina K, Maekawa N, Obara H: Lidocaine attenuates hyperoxic lung injury in rabbits. *Acta Anaesthesiol Scand* 1996; 40:318-25
 28. Cassuto J, Nellgard P, Stage L, Jonsson A: Amide local anesthetics reduce albumin extravasation in burn injuries. *ANESTHESIOLOGY* 1990; 72:302-7
 29. Kurose I, Suematsu M, Miura S, Fukumura D, Sekizuka E, Nagata H, Oshio C, Tsuchiya M: Oxyradical formation from leukocytes during endotoxin-induced microcirculatory disturbance in rat mesentery-attenuating effect of cetraxate. *Toxicol Appl Pharmacol* 1993; 120:37-44
 30. Granger DN, Kubes P: The microcirculation and inflammation: modulation of leukocyte-endothelial cell adhesion. *J Leukocyte Biol* 1994; 55:662-75
 31. Eriksson AS, Sinclair R, Cassuto J, Thomsen P: Influence of lidocaine on leukocyte function in the surgical wound. *ANESTHESIOLOGY* 1992; 77:74-8
 32. Suzuki M, Asako H, Kubes P: Neutrophil-derived oxidants promote leukocyte adherence in postcapillary venules. *Microvasc Res* 1991; 42:125-38
 33. Becker M, Menger MD, Lehr HA: Heparin-released superoxide dismutase inhibits postschemic leukocyte adhesion to venular endothelium. *Am J Physiol* 1994; 267:H925-30
 34. Mikawa K, Nishina K, Maekawa N, Takao Y, Yaku H, Obara H: Effect of lidocaine pretreatment on endotoxin-induced lung injury in rabbits. *ANESTHESIOLOGY* 1994; 81:689-99
 35. Seeman P: The membrane actions of anesthetics and tranquilizers. *Pharmacol Rev* 1972; 24:583-655
 36. Strichartz GR: The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. *J Gen Physiol* 1973; 62:37-57
 37. Weissmann G, Smolen JE, Korchak HM: Release of inflammatory mediators from stimulated neutrophils. *N Engl J Med* 1980; 303:27-34
 38. Kubes P, Suzuki M, Granger DN: Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci U S A* 1991; 88:4651-5
 39. Nishida J, McCuskey RS, McDonnell D, Fox ES: Protective role of NO in hepatic microcirculatory dysfunction during endotoxemia. *Am J Physiol* 1994; 267:G1135-41
 40. Mamiya K, Tomoda MK, Edashige K, Ueda W, Manabe M: Local anesthetics enhance nitric oxide production by human peripheral neutrophils. *Physiol Chem Phys Med NMR* 1995; 27:111-9
 41. Asher EF, Alsip NL, Zhang PY, Harris PD: Alteration of arteriolar responses to serotonin by two intravenous anesthetics. *J Vasc Res* 1992; 29:322-9
 42. Rimbäck G, Cassuto J, Wallin G, Westlander G: Inhibition of peritonitis by amide local anesthetics. *ANESTHESIOLOGY* 1988; 69: 881-6
 43. Yi ES, Ulich TR: Endotoxin, interleukin-1, and tumor necrosis factor cause neutrophil-dependent microvascular leakage in postcapillary venules. *Am J Pathol* 1992; 140:659-63
 44. Grega GJ, Adamski SW: Differential effects of inhibitors of cellular function on inflammatory mediator-stimulated increases in vascular permeability. *Microcirc Endothelium Lymphatics* 1991; 7:217-44
 45. Edwards MJ, Heniford BT, Miller FN: Mast cell degranulation inhibits IL-2-induced microvascular protein leakage. *J Surg Res* 1992; 52:429-35
 46. Taniguchi T, Shibata K, Yamamoto K, Kobayashi T, Saito K, Nakanuma Y: Lidocaine attenuates the hypotensive and inflammatory responses to endotoxemia in rabbits. *Crit Care Med* 1996; 24: 642-6