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Epidural Anesthesia Retards Intestinal Acidosis and Reduces Portal Vein Endotoxin Concentrations during Progressive Hypoxia in Rabbits

Kimiaki Ai, MD, Yoshifumi Kotake, MD,* Tomoyuki Satoh, MD,* Ryohei Serita, MD,* Junzo Takeda, MD,† Hiroshi Morisaki, MD‡*

Background: **Because it is postulated that gut is important *via* bacterial translocation in the development of the systemic inflammatory response and multiple organ dysfunction, the preservation of gut integrity is a therapeutic goal for physicians who care for critically ill patients. The aim of the current study was to evaluate whether epidural anesthesia prevented gut injury and subsequent translocation of endotoxin during acute progressive hypoxia in rabbits.**

Methods: **After the placement of an epidural catheter, 18 male rabbits, anesthetized with buprenorphine–midazolam, were allocated randomly to two groups: 0.5% lidocaine (group E) and saline (group C) groups. The solutions (0.4 ml/kg) were injected epidurally, followed by continuous infusion (0.1 $ml \cdot kg^{-1} \cdot h^{-1}$) during the study period. Portal blood flow, portal endotoxin concentrations, and intramucosal pH (pHi) of the ileum were measured at baseline and during two stages of progressive hypoxia (fraction of inspired oxygen [F_{IO_2}] = 0.15 and 0.10).**

Results: **In both study groups, the portal blood flow was preserved to a similar extent during acute hypoxia. However, pHi was reduced to a lesser extent in group E (7.33 ± 0.12 *versus* 7.22 ± 0.12 at an F_{IO_2} of 0.15 and 7.13 ± 0.15 *versus* 7.03 ± 0.12 at an F_{IO_2} of 0.10; mean ± SD, $P < 0.01$), concurrently with lower portal endotoxin concentrations ($P < 0.05$) compared with group C.**

Conclusions: **The current study showed that epidural anesthesia slowed the progression of intestinal ischemia during acute hypoxia, subsequently preventing translocation of endotoxin through the gut mucosa.**

THERE is increasing evidence that the gut, anatomically susceptible to oxygen lack, is a an origin of microorganisms or toxins as a result of the loss of the gut barrier function, which subsequently evokes the discharges of proinflammatory mediators and multiple organ dysfunction syndrome (MODS).[1–3] Therefore, preservation of functional integrity of gut in critically ill patients is consequential; however, few approaches are recognized as clinically useful to prevent the progression of gut injury.[4–6]

Because of its potential analgesic effects, combined epidural anesthesia and analgesia has been considered as a clinical strategy to improve the mortality rate in high-risk postsurgical patients.[7,8] Clinical studies showed that its application reduced the incidence of postoperative pulmonary complications and thromboembolism,[7] facilitated the recovery of gastrointestinal motility,[9] and preserved postsurgical immune function.[10] Although few studies have addressed whether epidural anesthesia *per se* improves oxygen use to preserve intestinal barrier function, some evidence in the literature supports the plausibility of this postulate. For example, epidural anesthesia prevented the progression of intestinal mucosal acidosis during major abdominal surgery.[11] In addition, epidural anesthesia has been shown to increase splanchnic venous capacity by depressing sympathetic nerve activity in a rabbit model.[12] Thus, the application of epidural anesthesia is likely to reduce arterial tone, which regulates villus microcirculation of the gut. The latter investigators showed that vasoconstrictive responses of splanchnic circulation to baroreceptor stimulation were attenuated by the use of thoracic epidural anesthesia.[13] Therefore, we tested the hypothesis that epidural anesthesia preserved functional integrity of the gut during acute progression of hypoxic stress in a rabbit model. In the current study, we found that the use of epidural anesthesia slowed the progression of intramucosal acidosis and translocation of endotoxin during hypoxia, indicating that epidural anesthesia preserved gut integrity during hypoxic injury.

Materials and Methods

This protocol was approved by the Keio University Council on Animal Care in accordance with the guidelines of the National Institutes of Health.

Preparatory Surgery

Eighteen healthy rabbits (Japanese White, male, SEA-SCO, Saitama, Japan), weighing 2.0–2.7 kg (average, 2.2 kg), were fasted for 24 h and underwent instrumentation during inhalation anesthesia. After 3 to 4% sevoflurane inhalation in oxygen (3 to 4 l/min) *via* face mask, the rabbits underwent tracheostomy and intravenous catheter insertion into a marginal ear vein. The rabbits underwent mechanical ventilation to maintain normocapnia (peak inspiratory pressure, 12–15 cm H_2O and 10–12 breaths/min) using an intensive care unit–type

* Instructor, † Professor, ‡ Assistant Professor.

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Address reprint requests to Dr. Morisaki: Department of Anesthesiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Address electronic mail to: anesmrsk@mc.med.keio.ac.jp. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

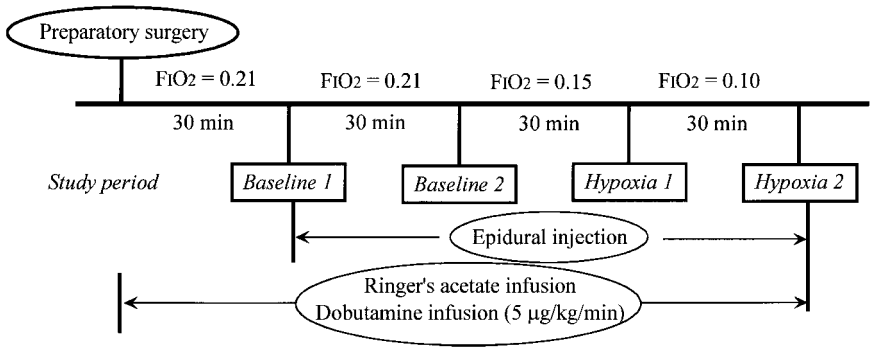

Fig. 1. Schematic drawing of experimental protocol.

ventilator (New Port E-100; New Port Medical Instruction Inc., Newport Beach, CA). An indwelling arterial catheter was inserted into the right carotid artery to monitor mean arterial pressure. According to the procedure described previously,[14] an epidural catheter was placed percutaneously using a 21-gauge Tuohy needle (Terumo Co., Tokyo, Japan) *via* the T12–L1 interspace during sterile conditions. To confirm the correct position of the epidural needle, the loss-of-resistance method was used. The catheter was advanced 3 to 4 cm into the epidural space in a cephalad direction and fixed to the skin with a silk suture. A midline abdominal incision was made, and a flexible catheter was inserted through the mesenteric vein to the distal portion of the portal vein for subsequent blood sampling. A perivascular probe, Transit-Time Ultrasound Flowmeter (T206; Transonic Systems Inc., Ithaca, New York), was attached around the portal vein for measurement of portal blood flow. A tonometer catheter (Tonometrics, Worcester, MA) was surgically inserted intraluminally into the terminal ileum *via* the ileocecal portion. After this preparatory surgery, inhalation anesthesia was discontinued, and a continuous 1-ml $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion mixture of buprenorphine (0.1 mg/ml), midazolam (2 mg/ml), and vecuronium (0.05 mg/ml) was performed during the study period to suppress vigorous spontaneous inspiratory efforts during hypoxia. Ringer's acetate solution (10–12 ml/kg) was infused for 30 min and continuously administered at a rate of 4 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} concurrently with dobutamine infusion (5 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) during the study period.

Study Protocol

After baseline measurements (baseline stage 1), 18 rabbits were allocated randomly to two groups. Nine animals (group E) received a 0.4-ml/kg bolus injection of 0.5% lidocaine through the epidural catheter and, subsequently, a continuous epidural infusion of 0.1 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}, as described previously[13]; another nine animals (group C) received the same dose of normal saline during the study period. After a 30-min equilibration period, the baseline portal flow, the pHi, and other analyses described in the Specific Measurements and Calculations section were performed (baseline stage 2). By mixing air with 100% nitrogen through the oxygen blender of the ventilator, F_{IO_2} was reduced in two stages (F_{IO_2} = 0.15 and 0.10) while monitoring with use of an anesthetic gas analyzer (Ohmeda 5250RGM; BOC Health Care, Louisville, CO). In our pilot study, the lowest F_{IO_2} that could be tolerated in this model was 0.10. Hemoglobin concentrations and arterial oxygen saturations were measured at each stage to calculate oxygen content. The measurements were then repeated after a 30-min equilibration period at each hypoxic stage (fig. 1). After epidural injection of 0.4 ml/kg indocyanine green, rabbits were killed by injection of intravenous pentobarbital (100 mg), and the distribution of the dye in the epidural space was evaluated. If cephalic spread of dye along the spine was not observed, information about these rabbits was excluded from the data collection.

Measurement of Intramucosal pH

Gut intramucosal pH (pHi) was monitored using a tonometric method that was described previously.[15] The balloon of the sigmoid tonometer (Tonometrics), placed in the lumen of the terminal ileum, was filled with 3 ml normal saline. After 30 min equilibration, 1 ml normal saline was aspirated and discarded. The remaining 2 ml was aspirated and immediately analyzed for tissue pressure of carbon dioxide (Pt_{CO_2}) with use of a blood gas analyzer (Chiron 860 series, Chiron Diagnostics Corp., East Walpole, MA). An equilibration period of 30 min was allowed between tonometer saline solution loading and sampling for all measurements. The measured Pt_{CO_2}, together with simultaneously obtained arterial [HCO_3^-], were fitted to the Henderson-Hasselbalch equation for calculation of pHi according to the manufacturer instructions:

$$pHi = 6.1 + \log[HCO_3^-]/0.03 \times Pt_{CO_2}$$

where [HCO_3^-] is the arterial bicarbonate concentration, 6.1 is the dissociation constant of HCO_3^-, and 0.03 is the solubility of carbon dioxide in plasma.

Specific Measurements and Calculations

Arterial and portal vein pH, P_{CO_2}, and P_{O_2} and lactate concentrations were determined using the Chiron blood

Table 1. Effects of Two Levels of Progressive Hypoxia on Systemic Circulatory Variables

	Baseline 1	Baseline 2	Hypoxia 1	Hypoxia 2
Arterial O_2 tension (mmHg)				
Group C	83.4 ± 23.7	80.6 ± 14.4	45.5 ± 4.2†	36.5 ± 5.4†
Group E	84.4 ± 19.8	78.8 ± 15.6	44.1 ± 7.5†	34.9 ± 6.3†
Arterial O_2 content ($ml \cdot O_2^{-1} \cdot l^{-1}$)				
Group C	15.6 ± 1.8	16.7 ± 1.2	12.1 ± 0.9†	8.0 ± 2.1†
Group E	15.9 ± 1.8	15.1 ± 1.8	12.0 ± 1.2†	7.6 ± 1.5†
Mean arterial pressure (mmHg)				
Group C	91 ± 12	83 ± 9	78 ± 12	62 ± 21‡
Group E	91 ± 6	72 ± 9*	77 ± 9	66 ± 12‡
Heart rate (beats/min)				
Group C	250 ± 66	293 ± 45	272 ± 57	252 ± 57
Group E	246 ± 54	273 ± 42	259 ± 63	248 ± 60
Arterial pH				
Group C	7.35 ± 0.06	7.38 ± 0.06	7.33 ± 0.06	7.16 ± 0.09‡
Group E	7.39 ± 0.06	7.37 ± 0.06	7.38 ± 0.06	7.19 ± 0.06‡
Arterial hematocrit (%)				
Group C	35 ± 3	37 ± 3	37 ± 3	33 ± 3
Group E	36 ± 3	32 ± 3	33 ± 3	33 ± 3
Arterial lactate (mM)				
Group C	4.1 ± 2.4	3.3 ± 2.1	6.0 ± 2.1	13.6 ± 3.0‡
Group E	3.9 ± 1.8	3.2 ± 1.8	4.9 ± 2.4	13.2 ± 4.8‡

Data are expressed as mean ± SD. * $P < 0.01$ *versus* group C, † $P < 0.01$ *versus* baseline 2 (reports the hypoxia stage effect), ‡ $P < 0.05$.
O_2 = oxygen.

gas analyzer. Hemoglobin concentration and hemoglobin oxygen saturation were measured using a cooximeter (OSM3; Radiometer, Copenhagen, Denmark). The splanchnic oxygen extraction ratio was calculated using the standard formula. After collection of arterial and portal blood during sterile conditions, the samples were centrifuged, and plasma was stored at −20°C until analysis. Plasma endotoxin concentration was measured using a synthetic chromogenic substrate method (Seikagaku-kogyo, Tokyo, Japan).[16] Lactate dehydrogenase and stable nitric oxide (NO) metabolites ($NO_2^- + NO_3^-$, NOx) were analyzed using spectrophotometric assay (Cayman, Detroit, MI) and interleukin 6 (IL-6) was analyzed using commercial immunoenzymometric assay kits (Amersham, Pharmacia Biotech, Buckinghamshire, UK). Plasma lidocaine concentrations were determined by means of fluorescence polarization immunoassay (TDX system; Abbot Laboratories, North Chicago, IL). Measurements of all parameters were performed in duplicate, and mean values were used for analysis.

Statistical Analysis

Data are expressed as mean ± standard deviation, unless otherwise specified. Analyses of variance with repeated measurements were used to evaluate the differences as shown by analysis using SPSS/9.0J (SPSS Inc., Chicago, IL) software for Windows (Microsoft, Redmond, CA). Separate analysis was performed if the interaction was statistically significant. When $P < 0.05$, the Scheffe multiple comparison test was applied to distinguish differences between measurement variables. If the data were not distributed normally, the Friedman test was used to evaluate pair-wise comparisons. Differences were considered to be statistically significant if $P < 0.05$.

Results

In the nine animals in each group, all stages of hypoxia occurred. Plasma lidocaine concentrations in group E were all less than 1.0 μg/ml. At postmortem examination after the final stage of the hypoxia study, correct placement of the epidural catheter in each animal was confirmed.

Systemic Effects of Progressive Hypoxia

Table 1 shows the changes of systemic hemodynamics and oxygen metabolism during acute hypoxia. Arterial Po_2 (Pao_2) and arterial oxygen content (Cao_2) decreased linearly to a similar extent during the hypoxia study periods. After epidural injection of lidocaine in group E, mean arterial pressure was significantly decreased, compared with that of group C. A significant hypoxia effect indicated that mean arterial pressure gradually was depressed during the hypoxia study periods in both groups. Heart rates were not statistically changed during the study period in both groups. Arterial pH and hematocrit concentration were not different between the groups during the study periods; however, a significant hypoxia effect indicated that arterial pH decreased hypoxia to a similar extent during acute progression. Arterial lactate concentrations were not statistically changed at hypoxia stage 1 but were significantly increased at hypoxia stage 2, compared with the baseline stage 2 value in both study groups.

Table 2. Effects of Two Levels of Progressive Hypoxia on Splanchnic Circulatory Variables and pHi

	Baseline 1	Baseline 2	Hypoxia 1	Hypoxia 2
Portal blood flow (ml · min^{-1} · kg BW^{-1})				
Group C	27.9 ± 11.7	16.1 ± 5.4	14.5 ± 7.5	12.2 ± 6.9
Group E	32.9 ± 11.7	20.9 ± 8.4	19.4 ± 7.2	18.0 ± 6.6
Portal oxygen extraction ratio (%)				
Group C	27.8 ± 9.9	34.0 ± 6.9	50.6 ± 9.3*	62.9 ± 8.4*
Group E	28.8 ± 9.0	35.5 ± 5.1	58.4 ± 7.2*	69.9 ± 7.2*
Portal pH				
Group C	7.34 ± 0.06	7.34 ± 0.06	7.28 ± 0.06	7.11 ± 0.09*
Group E	7.37 ± 0.06	7.34 ± 0.06	7.33 ± 0.06	7.11 ± 0.12*
Portal lactate (mM)				
Group C	4.4 ± 2.4	3.3 ± 1.8	5.7 ± 2.4*	12.4 ± 5.1†
Group E	4.1 ± 1.8	3.5 ± 1.8	5.3 ± 2.1*	12.4 ± 4.5†
pHi				
Group C	7.34 ± 0.11	7.32 ± 0.12	7.22 ± 0.12†	7.03 ± 0.12†
Group E	7.31 ± 0.08	7.29 ± 0.06	7.33 ± 0.12‡	7.13 ± 0.15†‡

Data are expressed as mean ± SD. * $P < 0.05$, † $P < 0.01$ *versus* baseline 2, ‡ $P < 0.01$ *versus* group C.
pHi = intramucosal pH.

Splanchnic Effects of Progressive Hypoxia

Table 2 shows the parameters of splanchnic circulation during the acute progression of hypoxia. Portal blood flow (indexed by kilogram–body weight) was not significantly changed in either group during the study periods. Simultaneously, the splanchnic oxygen extraction ratio, which was comparable at the two baseline studies, doubled in both study groups during hypoxia stage 2. Portal lactate concentrations, which were slightly increased at baseline stage 2 compared with the normal range (less than 2.0 mM), increased significantly to a similar extent during the hypoxia stages in both groups. Slight depression of portal blood flow and lactate concentrations, concurrent with a mild increase of the splanchnic oxygen extraction ratio, from the baseline 1 stage to the baseline 2 stage in group C suggests that the animals recovered from substantial effects of preparatory surgery at baseline stage 2. Conversely, the value of pHi behaved in a different manner between the two groups. The values of pHi in group C were progressively depressed during the two hypoxic stages, whereas those in group E remained unchanged at hypoxia stage 1, compared with baseline stage 2, and significantly decreased, but to a lesser extent, at hypoxia stage 2 compared with group C ($P < 0.05$). That is, pHi in group E was well-preserved without significant differences in portal blood flow during progressive hypoxia. To verify that the change of pHi was not caused by systemic acidosis, we further evaluated the P_{CO_2} gap between Pa_{CO_2} and Pt_{CO_2} during the hypoxic stages. We found that a P_{CO_2} gap in group C was significantly greater at hypoxia stage 2 than was the gap in group E (10.6 ± 1.9 *versus* 4.2 ± 2.1; $P < 0.05$), indicating that the pHi behavior during acute hypoxia was not caused by profound systemic acidosis but mainly by intestinal ischemia.

Changes of Biochemical Parameters

Table 3 shows the changes of mediators in arterial and portal blood during the study periods. Arterial concentrations of IL-6 in group C were significantly higher during the study periods from baseline stage 1; however, the same fluid resuscitation with use of dobutamine infusion was performed after randomization and preparatory surgery. IL-6 concentrations were increased in both study groups during hypoxia stage 2 ($P < 0.05$). Conversely, arterial and portal NOx concentrations were not significantly changed during the study period. In addition, arterial and portal lactate dehydrogenase concentrations in group C remained unchanged during the hypoxia study periods, indicating that significant destruction of splanchnic tissue was not obvious during acute hypoxia. To evaluate the changes of gut mucosal permeability against endotoxin, we measured portal concentrations of endotoxin at each experimental stage. Because the data were not distributed normally, the results were expressed as the median and range in table 3. The concentration of portal endotoxin in group E remained constant, whereas this marker in group C showed a significant increase during hypoxia stage 2 compared with the baseline 2 period ($P < 0.05$). In addition, during the hypoxia periods, endotoxin concentrations in group E were significantly lower than those in group C ($P < 0.05$), indicating that translocation of endotoxin through the gut mucosal layer was diminished in group E during the progression of acute hypoxia.

Discussion

The current study shows that epidural anesthesia preserves pHi of the gut during progressive hypoxia, subsequently preventing the elevation of portal endotoxin concentrations, possibly as a result of the reduction of

Table 3. Effects of Two Levels of Progressive Hypoxia on Biochemical Markers and Portal Endotoxin Concentrations

		Baseline 1	Baseline 2	Hypoxia 1	Hypoxia 2
Interleukin-6 (pg/ml)					
Group C	Arterial	41.6 ± 11.0	36.7 ± 8.5	35.1 ± 9.3	41.4 ± 12.3
	Portal	53.4 ± 14.9	56.5 ± 21.0	56.3 ± 31.1	85.1 ± 14.9†
Group E	Arterial	18.9 ± 4.6*	13.1 ± 3.9*	16.8 ± 8.2*	13.1 ± 4.2*
	Portal	24.7 ± 6.1	18.0 ± 5.3	26.0 ± 8.5	54.1 ± 8.5†
NOx (nmol/ml)					
Group C	Arterial	76.8 ± 7.1	78.6 ± 9.6	74.7 ± 9.2	81.8 ± 11.7
	Portal	73.9 ± 8.2	81.9 ± 8.7	71.1 ± 8.7	79.9 ± 10.5
Group E	Arterial	98.8 ± 15.5	96.8 ± 16.8	94.3 ± 13.6	87.0 ± 12.4
	Portal	96.7 ± 13.8	95.6 ± 13.8	88.3 ± 13.0	90.0 ± 13.3
Lactate dehydrogenase (mM)					
Group C	Arterial	113 ± 10	122 ± 10	110 ± 12	135 ± 20
	Portal	121 ± 12	126 ± 12	138 ± 15	155 ± 30
Group E	Arterial	112 ± 11	106 ± 9	106 ± 9	116 ± 9
	Portal	91 ± 11	117 ± 10	111 ± 9	124 ± 9
Endotoxin					
Group C	Portal	55.6 (16.6–81.8)	48.7 (20.6–100.9)	57.9 (14.0–214.2)	64.9† (32.7–257.0)
Group E	Portal	50.6 (9.1–102.7)	48.7 (11.8–98.9)	35.6*† (16.2–80.7)	39.7*† (14.0–70.9)

Data are expressed as mean ± SD for interleukin-6, NOx and lactate dehydrogenase and median (range) for portal endotoxin levels. * $P < 0.05$ *versus* group C † $P < 0.05$ *versus* baseline 2.

NOx = nitric oxide metabolites.

"bacterial translocation." Since the plasma lidocaine concentration was low,[11,17] it is probable that epidural anesthesia, not systemically absorbed lidocaine, ameliorated mucosal ischemia caused by hypoxic hypoxia. Because of its anatomic characteristics and redistribution of blood flow, the gut mucosal layer is considered to be vulnerable to any type of reduction in oxygen delivery.[18,19] Because pHi is a valuable marker to reflect gut mucosa oxygenation and overall outcome of critically ill patients,[2,3,15] epidural anesthesia could be a therapeutic procedure to preserve the functional integrity of the gut during injury.

During acute hypoxia, circulatory compensatory responses occur at whole-body and individual organ levels.[19–21] The splanchnic oxygen extraction ratio of the gut in both study groups increased to 62–70%, which was comparable with the critical concentration previously described.[22] Furthermore, in contrast to vital organs such as the heart or the brain, splanchnic microvascular resistance is increased by elevated tones of the arteriole or precapillary sphincter, resulting in the redistribution of blood flow away from the gut mucosa.[23] Epidural anesthesia may modulate such alterations of microvascular tones as a result of hypoxia in the splanchnic circulation, which is richly supplied with sympathetic nerves,[24] subsequently slowing the progression of intramucosal acidosis. It also may suppress the physiologic response to vasoconstrictive mediators or other local neural mechanisms during hypoxic injury. Alternatively, epidural anesthesia may modify immunologic responses such as leukocyte adhesion with microvascular endothelium, considered to be the crucial first step of inflammatory tissue injury.[25,26] Microvascular entrapment of activated leukocytes increases vascular resistance, possibly resulting in the exaggeration of ischemia. Such activation of leukocytes could be modified by the application of epidural anesthesia *in vivo*.[25] In addition, epidural anesthesia may augment intestinal motility during acute hypoxia. If bowel motility returned more promptly in group E after laparotomy, as described previously,[9] the microcirculatory alterations might become more efficient. Finally, epidural anesthesia may minimize the formation of microemboli, possibly disturbing the capillary network in the mucosal villus. Previous reports showed that epidural anesthesia induced multifactorial benefits for the host coagulation systems by enhancing fibrinolytic activity[27] or by decreasing postoperative increases in platelet aggregation.[7]

Plasma concentrations of endotoxin in splanchnic circulation do not always mirror the severity of gut mucosal injury, the lower concentrations seen in animals administered epidural anesthesia suggest that barrier function was better preserved. Conversely, the lack of differences in portal lactate dehydrogenase concentrations during hypoxia suggested that the cellular structure of the gut was not significantly damaged in the two groups. Because bacterial translocation is considered to be a sequela of functional, not structural, alterations of gut mucosa,[28] an accompanying increase in portal lactate dehydrogenase concentration may not be seen. Bacterial translocation as a result of the disruption of the gut barrier function is an early and crucial step for release of proinflammatory cytokines,[28,29] resulting in remote organ injury. Simultaneously, NO synthase is induced to maintain microcirculatory homeostasis during inflammatory injury. To evaluate the contribution of this pathway,

we evaluated the alterations of IL-6 and stable NO metabolites in portal and arterial blood. Although the precise role of IL-6 in the pathogenesis of systemic inflammatory responses must be established,[30] we found no significant effects of epidural anesthesia on the concentrations of this proinflammatory mediator. Because IL-6 production necessitates 1.5–3 h to reach the peak concentrations in the endotoxemic rat model,[30,31] the experiment may not have been of sufficient duration to permit the detection of any increases. Nevertheless, it is unlikely that this mediator is primarily responsible for the early phase of gut mucosa injury during acute hypoxia. NO, initially recognized as an endothelium-derived relaxing factor, has been implicated in the pathogenesis of ischemic tissue injury.[10] The measurements of NOx, such as NO_2^- and NO_3^- concentrations, to estimate NO production possibly reflect the severity of tissue injury.[10,32] In a hemorrhagic shock model, an increase of plasma NOx concentration was initiated at approximately at 1.5 h and was maximized at 4 h.[33] The decrease of intestinal blood flow as a result of hypoxia may induce a local increase in cytokines that can, in turn, cause up-regulation–inducible NO synthase expression, leading to a prolonged increase in tissue and plasma concentration of $NO_3^-NO_2^-$. The findings that plasma concentrations of NOx in arteries and portal veins are unchanged during progressive hypoxia suggest that up-regulation of NO was not significantly involved in this model.

There are some limitations to interpretation of the data herein. Because the pilot study showed that acute progression of hypoxia in this model caused significant depression of arterial pressures in both groups, we used volume infusion in combination with a low-dose dobutamine infusion during the study period. These interventions may contribute to the finding that no significant differences in hemodynamics between the groups were observed. Without such volume loading, depressive effects of hypoxia may be more profound than those of epidural anesthesia in this model. In addition, it can be argued that dobutamine infusion *per se* ameliorated the progression of intramucosal acidosis during acute hypoxia.[6] Although the effects of dobutamine on the microcirculation of the gut during hypoxia remains to be clarified, we believe that the intergroup differences in mucosal pHi and translocation of endotoxin can be attributed to the presence of epidural lidocaine. Furthermore, hemodynamic responses to acute progressive hypoxia might differ from the findings observed clinically.[20] In the current study, mechanical ventilation and paralysis may play a role in modulation of beneficial and deleterious hemodynamic responses to acute hypoxia: it can abolish the increase in respiratory work and the decreases in visceral and peripheral blood flow.[20] Therefore, deleterious effects of mechanical ventilation on hemodynamic parameters could be offset by benefits in reduction of systemic oxygen demands. Apparent differences of IL-6 concentrations between the two groups at the baseline periods might evoke caution when interpreting the data. Although the rabbits were randomized and the preparatory surgeries were performed in the same manner, the behavior of IL-6 in the experimental animals may not be comparable. Finally, some may question whether a decreased pHi measured using tonometry always indicates tissue hypoxia.[34] It is possible that the measurements that were obtained using normal saline and that were performed using the standard gas analyzer can induce significant error in the data.[35,36] In the current study, we duplicated the measurement of pHi in each stage by using a single gas analyzer, allowing us to eliminate such a source of errors.

In conclusion, the current study showed that epidural anesthesia slowed the progression of intestinal acidosis and subsequent translocation of endotoxin during acute hypoxia. The data presented do not define the responsible mechanisms, but indicate that epidural anesthesia may have therapeutic effects in addition to analgesic effects.

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