Sepsis Worsening Vascular Hyporeactivity of the Superior Mesenteric Artery in Portal Vein-ligated Rats

Wei-Chih Liao1,2, Ming-Chih Hou1,2*, Guci-Jane Wang3, Kwok-Woon Yu1,4, Fa-Yauh Lee1,2, Han-Chieh Lin1,2, Shou-Dong Lee1,2

1National Yang-Ming University School of Medicine; Departments of 2Gastroenterology and 4Infectious Disease, Department of Internal Medicine, Taipei Veterans General Hospital; 3National Research Institute of Chinese Medicine, Taipei, Taiwan, R.O.C.

Background: Vascular hyporeactivity is observed in portal hypertensive animals and septic rats. The objective of this study was to investigate whether impairment of superior mesenteric artery vascular contractility in the portal hypertensive rat was further impaired after sepsis.

Methods: Sepsis was induced by cecum ligation and puncture (CLP) in male portal hypertensive Sprague-Dawley rats that had been subjected to portal vein ligation (PVL) for 14 days. Hemodynamic studies, isolated vascular ring studies, microbiological studies, and plasma nitrite/nitrate measurements were performed 2, 6, and 18 hours after CLP. An additional group of PVL rats received prophylactic imipenem (10 mg intravenously for 1 hour) before CLP and then were studied 6 hours after CLP.

Results: Mean arterial pressure and heart rate of PVL rats were significantly decreased shortly after CLP. CLP caused further nitric oxide production and vascular hyporesponsiveness 6 and 18 hours after CLP compared with the baseline portal hypertensive group. Vascular hyporeactivity was corrected by N-nitro-L-arginine methyl ester + 1400W (1400W is N-(3-aminomethyl)benzyl)acetamidine hydrochloride, a selective inducible nitric oxide synthase inhibitor). Prophylactic imipenem did not alter nitric oxide production or vascular contractility after sepsis induced by CLP.

Conclusion: Our study showed that vascular contractility in portal hypertensive rats is further impaired soon after CLP-induced sepsis. [J Chin Med Assoc 2010;73(9):462–470]

Key Words: portal hypertension, sepsis, vascular contractility

Introduction

Portal hypertension is characterized by decreased vascular resistance and increased blood flow in the splanchnic and systemic circulation in humans and experimental models.1,2 Decreased vascular reactivity to vasopressors (e.g. phenylephrine, vasopressin, or angiotensin II) is mainly due to overproduction of vasodilators.3–6 Nitric oxide (NO) is the main vasodilator that is overproduced.7,8 Pharmacological treatment frequently fails to control acute esophageal varices bleeding in patients with infections.9,10 During sepsis, it has been proposed that response failure is due to more pronounced NO production.11,12 Although impaired vascular reactivity to vasopressors has been observed in septic rats,13,14 this phenomenon is not observed in portal hypertensive rats after lipopolysaccharide (LPS) challenge.15 Cecum ligation and puncture (CLP) is a live polymicrobial sepsis model.16 The kinetics and magnitude of cytokine production following CLP are significantly different from those of LPS challenge.17 It is unknown whether CLP-induced sepsis further elicits vascular hyporesponsiveness in the portal hypertensive rat, which already has blunted vascular reactivity caused by an overproduction of NO. Therefore, we implemented an animal model of sepsis superimposed on portal
hypertension by performing CLP in rats with portal vein ligation (PVL). The aim of this study was to evaluate vascular contractility in PVL rats following sepsis induced by CLP. Based on previous reports that imipenem effectively controls sepsis induced by CLP in rats,18,19 we also administrated imipenem before CLP to evaluate the effect of prophylactic antibiotics (ABX) on vascular responsiveness in PVL rats with CLP.

Methods

Animals

The experiments were performed in male Sprague-Dawley rats weighing 250–300 g. The rats were housed in Plexiglas cages with controlled temperature and humidity and were allowed free access to water and rat chow (Ralston Purina Co., St. Louis, MO, USA). The rats were anesthetized with ketamine hydrochloride (100 mg/kg body weight, intraperitoneal injection). After a midline incision was made, the portal vein was isolated and stenosis was created by means of a single ligature placed around both the portal vein and a blunt-ended 20-gauge needle. The needle was then removed, leaving a calibrated stenosis of the portal vein (PVL).20,21

In sham-operated animals, the portal vein was isolated, but no ligature was placed. The abdomen was then closed. Sham-operated rats were used as controls. After the operation, the animals were housed in plastic cages and allowed free access to rat food and water until 24 hours before CLP.

CLP

Fourteen days after PVL, the rats were anesthetized with ketamine hydrochloride (100 mg/kg body weight, intraperitoneal injection). An incision 2–3 cm long was made in the peritoneal cavity to expose the cecum. The cecum was ligated with 3-0 silk suture without occluding the lumen of the small or large bowel. A 19-gauge needle was then used to puncture the ligated cecum twice, which resulted in 4 holes in the cecum. A small amount of feces was gently expressed into the peritoneal space. The cecum was returned to the peritoneal cavity, and the incision was closed in 2 layers with a 3-0 silk running suture. Immediately after the procedure, the rats received 5 mL/100 g of normal saline subcutaneously and dorsally for resuscitation.16

Hemodynamic studies

In polymicrobial sepsis induced by CLP, the hemodynamic changes are characterized by an early, hyperdynamic phase (i.e. 2–10 hours) followed by a late, hypodynamic phase (greater than 16 hours).22–24 Although the hemodynamic changes occur as early as 2 hours after CLP, profound NO production by inducible NO synthase (iNOS) begins 5–6 hours after CLP.25–27 During the late phase, most parameters including mean arterial pressure, heart rate, and body temperature are lowest at 18 hours after CLP.24 In our preliminary study, all animals were dead 24 hours after CLP. Therefore, rats that survived PVL were divided into 3 groups in which the experiments were performed 2, 6, and 18 hours after CLP: PVL + CLP2 (n = 8, beginning of early sepsis), PVL + CLP6 (n = 8, beginning of NO production), and PVL + CLP18 (n = 8, late phase of sepsis). The rats were anesthetized with ketamine hydrochloride (100 mg/kg body weight, intraperitoneal injection). The femoral artery was cannulated with a PE-50 catheter, which was then attached to a pressure transducer for the measurement of mean arterial pressure.28 The abdomen was then opened. Portal vein pressure was measured indirectly with direct splenic puncture (splenic pulp pressure). Sterile swabs were passed over the parietal peritoneum and plated. Hemodynamic studies were also performed in sham-operated rats (n = 8), which served as normal controls, and in PVL rats without CLP (n = 8) as portal hypertensive controls. At completion of the baseline hemodynamic measurement, the superior mesenteric artery was carefully excised for vascular ring studies. Blood samples (2 mL) from the femoral arterial catheter were collected into blood culture bottles. The remaining samples were collected into chilled, heparinized test tubes, which were then immediately centrifuged at 3,000 rpm at 4°C for 20 minutes. The supernatant was frozen for subsequent measurement of serum NO concentrations.29

Isolated vascular ring studies

The superior mesenteric artery from each rat was cut into 5-mm rings. The rings were then mounted between 2 stainless steel wires in a 15-mL jacketed organ chamber containing modified Krebs solution (0.12 mol/L NaCl, 4.7 mmol/L KCl, 2.4 mmol/L MgSO4, 1.2 mmol/L KH2PO4, 11 mmol/L glucose, 25 mmol/L NaHCO3, and 1.25 mmol CaCl2 bubbled with 95% O2 and 5% CO2 at 37°C). After equilibration, the vascular rings were stretched with an initial passive force of 1 g. One wire was fixed to a brass manipulator and the other was attached to an isometric force transducer (model FT 03; Grass Instruments Co., Quincy, MA, USA) and a polygraph (models 7 and 7E; Grass Instruments Co.) for the continuous recording of tension. Eight vascular rings were examined in parallel. After the rings were equilibrated for 90 minutes, KCl (0.6 M) was added to the tissue bath to check tissue viability. The presence of endothelium was
confirmed by the addition of acetylcholine (10 μmol/L). The drug was washed out and the tissue was allowed to return to a baseline level. The cumulative dose-response curve of phenylephrine (10^{-11} to 10^{-5} M) was then determined. The vessels were washed extensively before adding the NOS inhibitor N-nitro-L-arginine methyl ester (L-NAME; final concentration, 100 μmol/L) for 20 minutes, then the iNOS inhibitor 1400W (N-(3-(aminomethyl)benzyl) acetamidine hydrochloride; final concentration 30 μmol/L) for 30 minutes, and a combination of both L-NAME and 1400W. Determination of the cumulative dose-response curves for phenylephrine (10^{-11} to 10^{-5} M) was repeated. The tissue viability was again checked with KCl (0.6 M) at the end of the experiment. The vessel rings were then dried for 24 hours and weighed. The force of vascular contraction was standardized by tissue weight.29

**Microbiological study**

For blood cultures, 1 mL of blood was inoculated in standard blood culture bottles for aerobic and anaerobic microorganisms and then incubated in the corresponding automated system (BacT/Alert; Organon Teknika Corp., Durham, NC, USA). For peritoneal culture, samples were collected by passing a sterile swab over the peritoneum and then inoculated on a bi-plate containing sheep blood agar, cosin methylene blue medium and Brucella agar. The bi-plate was incubated at 37°C for 48 hours for aerobic microorganisms. The Brucella agar was incubated under anaerobic conditions in an anaerobic jar (Anaerocult A; Merck Ltd., Darmstadt, Germany). Subsequent identification of the bacterial isolates in positive cultures was performed according to standard microbiological methods.31

**Effect of ABX**

To study the effect of ABX, a single dose of imipenem was given (10 mg intravenously) to a selected group of rats 1 hour before CLP (PVL + ABX + CLP6). The hemodynamic study, microbiology study, and isolated vascular ring study were performed 6 hours after CLP.

**Measurement of plasma NO**

Plasma concentrations of stable NO were measured using colorimetric assays (Caymen Chemicals, Ann Arbor, MI, USA). In serum, the final products of NO in vitro are nitrite (NO_{2}^{-}) and nitrate (NO_{3}^{-}). In brief, the nitrate in the sample was reduced to nitrite by adding nitrate reductase. The nitrite was converted to a deep purple azo compound with the addition of a Greiss reagent and subsequently measured by spectrophotometry (Bio-Tek EL331 Microplate Autoreader; Bio-Tek, Winooski, VT, USA) at 550 nm.14

**Statistical analysis**

Continuous variables were expressed as group medians (range) and compared between groups using a Wilcoxon 2-sample test or Kruskal-Wallis nonparametric test. Data used to plot dose-response curves were the median (range) contraction induced at each concentration of the drug. The dose-response curves were compared by the extra sum of squares F test of EC_{50}(logM). Categorical variables were examined using Fisher’s exact test. Significance was set at p<0.05. Statistical and graphical analyses were carried out using PRISM 5 (2006; GraphPad Software Inc., San Diego, CA, USA) for Windows.

**Results**

**Hemodynamic studies**

Hemodynamic data are shown in Table 1. After 14 days of PVL, portal hypertension was evident as shown by significantly elevated splenic pulp pressure. Mean

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mmHg)</th>
<th>HR (bpm)</th>
<th>PP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n = 8)</td>
<td>125.76 (120.37–136.20)</td>
<td>325.5 (222.0–378.7)</td>
<td>6.94 (5.59–7.94)</td>
</tr>
<tr>
<td>PVL (n = 8)</td>
<td>110.60 (96.80–118.20)</td>
<td>404.0 (358.9–404.0)</td>
<td>13.75 (12.0–16.0)</td>
</tr>
<tr>
<td>PVL + CLP2 (n = 8)</td>
<td>89.15 (82.00–100.30)</td>
<td>290.6 (268.3–374.4)</td>
<td>15.89 (12.57–15.47)</td>
</tr>
<tr>
<td>PVL + CLP6 (n = 8)</td>
<td>82.05 (63.70–91.60)</td>
<td>293.5 (291.6–358.0)</td>
<td>16.51 (14.12–22.64)</td>
</tr>
<tr>
<td>PVL + CLP18 (n = 8)</td>
<td>70.52 (58.50–72.68)</td>
<td>278.0 (232.1–372.1)</td>
<td>14.89 (12.06–19.71)</td>
</tr>
<tr>
<td>PVL + ABX + CLP6 (n = 8)</td>
<td>77.18 (68.10–77.20)</td>
<td>289.9 (256.3–322.1)</td>
<td>16.51 (14.12–22.64)</td>
</tr>
</tbody>
</table>

*Data are presented as median (range); †CLPx hemodynamic study was performed x hours after cecum ligation and puncture. MAP = mean arterial pressure; HR = heart rate; PP = pulp pressure; PVL = portal vein ligation; CLP = cecum ligation and puncture; ABX = antibiotics.

NOTES. (1) Results of PVL were compared with those of sham by Wilcoxon 2-sample test. Significant differences were found in MAP (p = 0.001), HR (p = 0.003), and PP (p = 0.001) after PVL. (2) The values were compared within PVL + CLP groups by Kruskal-Wallis test, and there were significant differences in MAP (p = 0.001) and HR (p = 0.003), but no significant differences in PP (p = 0.288), among groups. (3) There were no significant differences in MAP, HR and PP between PVL + CLP6 and PVL + ABX + CLP6 by Wilcoxon 2-sample test.
artrial pressure was significantly decreased and heart rate was significantly increased after PVL. In portal hypertensive animals that had received CLP (PVL + CLP), both mean arterial pressure and heart rate were significantly lower than those in PVL controls. The splenic pulp pressures were not significantly different between PVL rats with and without CLP. The hemodynamics endpoints of PVL + CLP6 rats that had received ABX (PVL + ABX + CLP6) were not significantly different from those of rats that had not received ABX.

**Microbiological study**
Laparotomy in the PVL + CLP group revealed a pale necrotic cecum and 1–2 mL of cloudy fluid in the peritoneum. Peritoneal cultures from these animals were all positive. Most peritoneal cultures grew mixed microorganisms, mainly *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Lactobacillus* spp., *Bacillus* spp., and *Bacteroides fragilis*. Blood cultures obtained from these animals were all positive. The blood culture rate was significantly lower in the ABX group (PVL + ABX + CLP6) compared with the PVL + CLP6 group (culture rate: 8/8 vs. 2/8; *p* = 0.007). However, ABX did not produce a statistically different peritoneal culture rate (culture rate: 8/8 vs. 6/8; *p* = 0.233).

**Isolated vascular ring studies**
The contractile response of the superior mesenteric artery in PVL rats is shown in Figure 1. A significant vascular hyporesponsiveness to phenylephrine was observed in PVL controls rats compared with sham-operated rats (Figure 1A). Treatment with L-NAME + 1400W resulted in a shift to the left in the dose-response curves of sham-operated rats. The sham + L-NAME and sham + L-NAME + 1400W groups had a significantly higher maximal contraction than the sham alone group [maximal contraction (g): sham + L-NAME vs. sham: 4.40 (3.38–4.67) vs. 3.85 (3.51–4.34), *p* < 0.001; sham + L-NAME + 1400W vs. sham: 4.28 (3.86–4.30) vs. 3.85 (3.51–4.34), *p* < 0.001]. The 1400W alone did not alter the dose-response curves of sham-operated rats (Figure 1B). After incubation with L-NAME + 1400W, but not 1400W alone, comparison of the dose-response curves for sham and PVL controls showed no significant difference (Figure 1C). The PVL + 1400W group had a significantly lower maximal contraction than the sham [maximal contraction (g): sham vs. PVL + 1400W: 3.85 (3.51–4.34) vs. 3.15 (2.70–3.64), *p* = 0.001]. These results indicate that vascular hyporesponsiveness to phenylephrine in PVL rats could be corrected by L-NAME, but not by 1400W.

**Contractile response in PVL rats after CLP**
The dose-response curves were not significantly different between PVL control (without CLP) and PVL + CLP2 rats (Figure 2A). However, 6 and 18 hours after CLP (PVL + CLP6 and PVL + CLP18), the dose-response curves for the superior mesenteric artery were significantly lower than those in the PVL controls. These results indicate that the vascular response to phenylephrine in PVL starts to be attenuated 2–6 hours after CLP-induced sepsis.

**Effects of NOS inhibition and ABX**
After incubation with L-NAME with or without 1400W, the dose-response curves for PVL + CLP2 rats shifted to the left, and vascular contractility was restored to that of PVL controls treated with L-NAME (Figure 2B). Incubation with 1400W alone did not alter the vascular contractility of PVL + CLP2 rats. In PVL + CLP6 and PVL + CLP18 rats, which already had further impaired vascular contractility after CLP, the dose-response curves also shifted to the left, but were still lower than the curves for the PVL control rats treated with L-NAME or 1400W alone (Figures 2C and 2D). The dose-response curves shifted even further to the left following incubation with L-NAME and 1400W (PVL + CLP6 + L-NAME + 1400W vs. PVL + CLP6 + L-NAME, *p* = 0.031; PVL + CLP18 + L-NAME + 1400W vs. PVL + CLP18 + L-NAME, *p* = 0.006). L-NAME combined with 1400W also restored the contractility of PVL + CLP6 rats to that observed for PVL controls treated with L-NAME. Although the dose-response curves of PVL + CLP18 rats also shifted further to the left after incubation with a combination of L-NAME and 1400W, they were still lower than those of PVL controls treated with L-NAME alone. The dose-response curve of PVL + ABX + CLP6 rats showed no significant difference compared with the dose-response curve of PVL + CLP6 rats (PVL + CLP6 vs. PVL + ABX + CLP6, *p* = 0.58; Figure 3).

**Effects of PVL and CLP on plasma NO$_3^−$/NO$_2^−$**
PVL caused a significant increase in plasma NO$_3^−$/NO$_2^−$ concentrations. Two hours after the onset of sepsis induced by CLP in PVL rats, there was no additional increase in plasma NO$_3^−$/NO$_2^−$ concentrations compared with the PVL control rats. Six hours after CLP in PVL rats, plasma NO$_3^−$/NO$_2^−$ concentrations increased further. The increase in plasma NO$_3^−$/NO$_2^−$ concentrations persisted for 18 hours following CLP (Figures 4 and 5). ABX did not cause a decrease in plasma NO$_3^−$/NO$_2^−$ concentrations 6 hours after CLP.
Figure 1. Dose-response curves of phenylephrine-induced contraction of the superior mesentery artery in portal vein-ligated (PVL) and sham-operated rats: (A) before; and (B, C) after incubation with N-nitro-L-arginine methyl ester (L-NAME) and 1400W.

Discussion

In the current study, hyporesponsiveness to phenylephrine in PVL rats was corrected with the use of a non-selective NOS inhibitor (L-NAME), which is consistent with previous studies. We found that the dose response curves of the sham + L-NAME or sham + L-NAME + 1400W groups were significantly higher than that of the sham group (Figure 1B). The hyperresponsive reaction resulted from existing physiological eNOS blocked by L-NAME. This result is compatible with that of a previous study. For more than 6 hours after CLP, vascular contractility was further impaired in portal hypertensive rats. Vascular hyporesponsiveness improved after incubation with L-NAME. These results indicate that a more pronounced NO production occurred in PVL rats than in sham-operated rats, which is consistent with previous non-portal hypertensive
Vascular reactivity in PVL rats with sepsis

A.

Sham (n = 8)
PVL (n = 8)
PVL + CLP2 (n = 8)
PVL + CLP6 (n = 8)
PVL + CLP18 (n = 8)

B.

p = 0.01
p = NS
p = 0.048
p < 0.001

Phenylephrine concentration (logM)

Contractility (g)

p = NS
p < 0.001

Phenylephrine concentration (logM)

Contractility (g)

(Contd)

This observation is supported by the finding of increased plasma concentrations of $\text{NO}_3^-/\text{NO}_2^-$ 6 hours after initiation of CLP, which is also consistent with previous studies. However, we found that the dose-response curves for PVL + CLP6 and PVL + CLP18 rats treated with L-NAME were still lower than those of PVL controls treated with L-NAME. A possible explanation for partial correction by L-NAME is that there was incomplete iNOS inhibition or involvement of mediators other than NO in the CLP-induced vascular hyporesponsiveness in PVL rats. We examined the former possibility with the potent and highly selective iNOS inhibitor 1400W. We found that L-NAME combined with 1400W almost completely restored vascular contractility in early sepsis in PVL rats. This observation provided further support for augmented NO overproduction by iNOS resulting in further vascular hyporesponsiveness in PVL rats after CLP. In the later stage of sepsis in PVL rats, contractility of the superior mesentery artery was strengthened by the combination of L-NAME and 1400W, but it was still lower than that observed for the PVL controls. In both the present and previous non-portal hypertensive studies, CLP caused a significant increase in plasma $\text{NO}_3^-/\text{NO}_2^-$ concentrations during early sepsis. We found that iNOS activity reached its maximum at the end of early sepsis, and there was no additional increase in plasma $\text{NO}_3^-/\text{NO}_2^-$ during late sepsis. These findings indicate that factors other than NO, such as direct muscle injury, may be involved in CLP-induced hyporesponsiveness in PVL rats during late sepsis.

However, Heller et al showed that in vitro vascular reactivity in the aorta of PVL rats did not decrease 5 hours after LPS administration. They found that because baseline NO overproduction by eNOS can inhibit iNOS activity after LPS administration, further impairment of vasoreactivity has not been observed in LPS-administered portal hypertensive rats. A high concentration of tumor necrosis factor-$\alpha$ might prevent the inhibition of iNOS induction by the aortic endothelium in portal hypertensive rats. In the LPS-challenged sepsis model, the tumor necrosis factor-$\alpha$ concentration peaks between 1.5 and 4 hours and declines thereafter. In contrast, the tumor necrosis factor-$\alpha$ concentration in the CLP model continues to increase at the 8-hour time point. The different pharmacokinetics of cytokines and vascular types (superior mesentery artery in our study and thoracic aorta...
Figure 2. (A) Dose-response curves of phenylephrine-induced contractility of the superior mesentery artery in portal vein-ligated (PVL) rats before and 2, 6, and 18 hours after cecum ligation and puncture (CLP). Dose-response curves of phenylephrine-induced contraction of the superior mesentery in PVL rats. (B) 2 hours, (C) 6 hours, and (D) 18 hours after CLP before and after incubation with N-nitro-L-arginine methyl ester (L-NAME) and 1400W.

Figure 3. Dose-response curves of phenylephrine-induced contractility of the superior mesentery artery in portal vein-ligated (PVL) rats 6 hours after cecum ligation and puncture (CLP) with or without antibiotics (ABX) 1 hour before CLP.

Figure 4. Plasma concentrations of NO$_3^-$/NO$_2^-$ in sham-operated and portal vein-ligated (PVL) rats before (control) and 2, 6, and 18 hours after cecum ligation and puncture (CLP) in PVL rats. Data are expressed as the median with range. *p < 0.05 vs. sham-operated; †p < 0.05 vs. PVL.
in Heller et al’s study) could be possible reasons for the discrepancy between the present model and Heller et al’s model. In contrast with the LPS challenge, CLP induces infection and local inflammation, which is soon accompanied by a cascade of systemic pathophysiological and immunological reactions. Gram-positive bacteria also cause a significant number of infections in cirrhotic patients. Gram-positive and Gram-negative bacteria more appropriately resemble a real infection in portal hypertensive patients in a CLP model than in an LPS-challenged model, in which only part of the cell wall component of Gram-negative bacteria is injected into the circulation.

Patients with portal hypertension and gastrointestinal bleeding are particularly susceptible to bacterial infection. In portal hypertensive patients, bacterial infection is independently associated with a failure to control bleeding, despite active treatment with vasoconstrictors such as terlipressin or somatostatin. Infection-induced NO overproduction has been suggested to possibly be a trigger of early variceal rebleeding through its antiplatelet effects. Based on the current observation of superior mesenteric artery hyporesponsiveness in septic PVL rats in vitro, we postulate that NO may have another role in the failure of pharmacological control of variceal bleeding in infected patients through a reduction in the responsiveness of the superior mesenteric artery to vasoactive agents.

In the current study, the amount of imipenem administered (10 mg intravenously 1 hour before CLP) was based on a dose used in a previous study to prevent intra-abdominal sepsis. However, in the current study, ABX did not alter the peritoneal culture rate, hemodynamic status, or sepsis-induced superior mesenteric artery hyporesponsiveness. It is possible that the comorbid status of portal hypertension makes rats more vulnerable to infection despite ABX. A higher dose of antibiotics and a longer duration of treatment (20 mg imipenem injected intramuscularly 1 hour before CLP, a second injection of 10 mg imipenem 2 hours after infection, and then 10 mg imipenem every 8 hours for 3 days) was used in a previous study to prevent sepsis. Although the survival rate improved, peritoneal abscess was still observed in 37% of the surviving animals. Therefore, it is not known whether a higher dose of antibiotics for a longer time could prevent a sepsis cascade in portal hypertensive rats.

In conclusion, we observed that vascular reactivity was further impaired soon after CLP-induced sepsis in portal hypertensive rats. Vascular hyporesponsiveness to vasoactive agents during sepsis should be taken into account when attempting to explain bacterial infection as a poor prognostic factor for control of variceal bleeding. However, further clinical studies are needed to validate this hypothesis.

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