Hepatic Blood Flow and Oxygen Consumption after Burn and Sepsis

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Background: **Alteration in the hepatic circulation after burn and in sepsis seems to be an essential component in the development of multiple organ failure.**

Methods: **Female pigs (n = 12, 20–25 kg) were instrumented with ultrasonic flow probes on the portal vein and the common hepatic artery. Catheters were inserted in the superior mesenteric and left hepatic veins. After 5 days, all animals were anesthetized and six of them received 40% total body surface area third-degree burn. A total of 100 μg/kg *Escherichia coli* LPS was intravenously administered at 18 hours after burn. All animals were studied for 42 hours.**

Results: **Thermal injury resulted in a 48% decrease in hepatic arterial blood flow despite maintenance of normal cardiac output, resulting in a fall in hepatic oxygen delivery rate. Portal venous blood flow showed a 32% increase at 4 hours after burn. Post-LPS portal blood flow was significantly reduced for a period of 8 hours (51% of baseline (bl), $p < 0.05$ analysis of variance [ANOVA]). The hepatic arterial blood supply was also significantly reduced (12–67% of bl, $p < 0.05$ ANOVA) during the first 4 hours after LPS, indicating loss of the hepatic arterial response. The following 12 hours, a hepatic reperfusion phase was observed with an elevation of the hepatic arterial blood flow to 152% of bl ($p < 0.05$ ANOVA). Postburn endotoxemia resulted in a significant decrease of hepatic oxygen delivery (88%) and hepatic oxygen consumption (79%). Although the burn injury did not affect the portal venous pressure, postburn endotoxemia caused a significant portal hypertension during a period of 8 hours (225% of bl, $p < 0.05$ ANOVA).**

Conclusion: **Postburn sepsis amplifies the selective vasconstrictive impact of thermal injury on hepatic arterial blood flow, yielding a pronounced ischemia/reperfusion injury, associated with a critical reduction of hepatic oxygen delivery and consumption. A postburn septic challenge induces portal hypertension, which may account for previously documented gut barrier dysfunction.**

Key Words: **Thermal trauma, Sepsis, Endotoxin, Hepatic ischemia, Hepatic reperfusion injury, Hepatic oxygen consumption, Portal hypertension.**

J Trauma. 2000;49:101–108.

Sepsis and multiple organ dysfunction syndrome remain to be the most common causes of the high morbidity and mortality rates after major burn injuries.[1–3] It has been postulated that the amplified reaction of the primed inflammatory response system of thermally injured patients to a subsequent insult, initiated by bacteria and their byproducts (endotoxins), is responsible for the typical pathophysiologic alterations seen in postinjury sepsis.[2] Although a clearly defined pathophysiologic mechanism has not yet been defined, the gastrointestinal tract has been postulated to be a major contributor to postburn sepsis.[4] The intestinal mucosal barrier normally prevents the enteric bacteria and their byproducts from escaping and reaching extraintestinal organs. However, under certain circumstances, the integrity of intestinal mucosa seems to be disrupted, allowing an exaggerated leaking of endogenous bacteria or endotoxins to the portal circulation; this is a process called bacterial translocation.[5,6]

As the hepatic reticuloendothelial system (Kupffer cells) seems to play a pivotal role in the clearance of translocating bacteria, endotoxin, or both, from the portal circulation,[7] impairment of this hepatic clearance function may potentiate systemic effects of gut barrier failure by allowing indigenous bacteria or endotoxin to reach the systemic circulation, where they potentiate systemic inflammatory responses.

Phagocytosis of bacteria and sequestering of endotoxin by hepatic Kupffer cells impose a high metabolic demand on the reticuloendothelial system.[8] Intermediary metabolism and energy production have an absolute dependence on oxygen. Because oxygen cannot be stored intracellularly, inadequate oxygen availability rapidly leads to cellular dysfunction and ultimately cell death with the net result being organ failure. Hence, the importance of the hepatic perfusion for the performance of Kupffer cells.

The present study was designed to define the hemodynamic response and the tissue perfusion of the liver to severe thermal injuries and postburn endotoxemia in a burn/endotoxin porcine model.

MATERIALS AND METHODS

The following experimental protocols were approved by the Animal Care and Use Committee of the University of Texas Medical Branch (ACUC 90–09-103). Twelve female mini-pigs, each weighing between 20 and 25 kg, were prepared surgically 5 days before the experiment. After an over-

Submitted for publication January 12, 1999.
Accepted for publication March 29, 2000.

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Presented at the 10th Annual Meeting of the Surgical Infection Society-Europe, May 29–31, 1997, Istanbul, Turkey.
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night fast, the pigs were sedated with intramuscular (i.m.) ketamine (10 mg/kg) and mechanically ventilated with 2 to 2.5% halothane after endotracheal intubation. A subcostal incision was performed. Transit time ultrasonic flow probes (4–10 mm, Transonic Systems, Inc., Ithaca, NY) were placed on the common hepatic artery and the portal vein. The 6.5 French catheters were positioned in the superior mesenteric vein and the left hepatic vein. Witzel jejunostomy was also performed by using a 12 French Foley catheter. The abdomen was closed in layers.

After surgery, the animals were kept in special recovery slings for 24 hours, then placed in runs for 5 days with free access to food and water. On the day of the experiment, the animals were reanesthetized, and through a neck incision, an arterial catheter was placed by means of the right common carotid artery into the abdominal aorta. A Swan-Ganz thermal dilution catheter (model 93 A-131–5F, American Edwards Laboratories, Anasco, PR) was positioned in the pulmonary artery through the right jugular vein. A 12 French Foley catheter was inserted in the urinary bladder.

The animals were kept in special slings for monitoring. All animals tolerated the slings well, without any signs of stress or need for sedation. Throughout the study, all animals received enteral feeding (Osmolite) at 25 mL/h and nothing per os. Baseline data were collected after complete recovery from anesthesia.

Pigs were randomly assigned into two groups: the burn/LPS group (n = 6) had a 40% total body surface area (TBSA) third-degree flame burn under general anesthesia as described above. The pigs were resuscitated according to the Parkland formula and received lactated Ringer's solution, 4 mL/kg/%TBSA burn, starting immediately after burn. Half of the fluid was given in the first 8 hours after burn and the remainder in the following 16 hours. Eighteen hours after burn, 100 μg/kg *Escherichia coli* lipopolysaccharide (0111:B4; Difco, Detroit, MI) was intravenously administered. During the second day of the experiment, burned animals received lactated Ringer's solution at 3,5 mL/m^2 burned area and 2 mL/kg per hour for daily maintenance. The sham group (n = 6) had a sham burn under anesthesia. Eighteen hours later the animals received the diluent (0.9% NaCl) used for the endotoxin. Lactated Ringer's solution was administered at a rate of 2 mL/kg per h for daily maintenance.

Mean arterial (MAP), central venous (CVP), and portal venous (PVP) pressures were measured by using transducers (P231D, Statham Gould, Oxnard, CA) that were connected to an Electronic Medicine Honeywell Recorder for electronically calculated mean pressures. Cardiac output (CO) was determined by the thermal dilution technique with a Swan-Ganz catheter and a cardiac output computer (model 9520, American Edwards Laboratories, Irvine, CA).

Hepatic arterial blood flow (Qh) and portal venous blood flow (Qp) were measured with transit time ultrasonic flow probes connected to a T101 ultrasonic meter (Transonic Systems, Inc.). Systemic and hepatic hemodynamics were measured and blood samples were drawn for determination of arterial, mixed venous, and hepatic blood gases at baseline and 14 consecutive time points, starting 1 hour after burn.

Systemic vascular resistance index (SVRI), hepatic arterial vascular resistance (HAVR), and hepatic portal vascular resistance (HPVR) were calculated with the following formulas: SVRI (dyne · s · cm^{-5}·m^2) = [(MAP - CVP) × 80]/CI; HAVR (dyne · s · cm^{-5}) = [(MAP - CVP) × 80]/Qh; HPVR (dyne · s · cm^{-5}) = [(PVP - CVP) × 80]/Qp.

Systemic O_2 delivery (Do_2), systemic O_2 consumption (Vo_2), hepatic O_2 delivery (hDo_2), and hepatic O_2 consumption (hVo_2) were calculated with the following formulas: $Do_2 = CI \times Cao_2 \times 10$ (mL/min per m^2); $Vo_2 = CI \times (Cao_2 - Cvo_2) \times 10$ (mL/min per m^2); $hDo_2 = Qh \times Cao_2/100$ (mL/min); $hVo_2 = Qh \times (Cao_2 - Cho_2)/100$ (mL/min), where CI = cardiac index (L/min per m^2), Cao_2 (arterial oxygen content, mL/dL) = (Hb × 1.34) Sao_2 + (Pao_2 × 0.0031), Cvo_2 (mixed venous oxygen content, mL/dL) = (Hb × 1.34) Svo_2 + (Pvo_2 × 0.0031), and Cho_2 (hepatic oxygen content, mL/dL) = (Hb × 1.34) Sho_2 + (Pho_2 × 0.0031). At the end of the 42 hours, animals were anesthetized with 10 mg/kg of intravenous ketamine and killed with 5 mL of intravenous saturated KCl.

The data are presented as mean ± SEM. Within group analysis was performed by the analysis of variance (ANOVA) for repeated measurements with the Dunnett's post hoc test. Between groups analysis was performed by ANOVA for factorial analysis with Bonferroni post hoc test. All p values of <0.05 were considered statistically significant.

RESULTS

Systemic Hemodynamics

Baseline hemodynamic measurements were similar in all groups. All animals survived the study period. Throughout the experiment, sham animals maintained their systemic (Figs. 1 and 2) hemodynamics within baseline range.

After thermal injury, CO showed a slight increase during the first 6 hours, returning to baseline 8 hours postburn (Fig. 1). This increase was associated with a concomitant fall in the systemic vascular resistance, whereas SVRI decreased to 78% of baseline level (Fig. 1). There were no significant differences in mean MAP, CVP, serial hematocrits (Hct), or urine production (UP) between the two groups (Figs. 2 and 3).

After administration of LPS, a typical biphasic response was observed. The hemodynamic alteration was more pronounced during the second phase, as after a marked drop of CO to 77% of baseline level, a hyperdynamic period began to be manifest 8 hours after endotoxin (Fig. 1). At this time point, SVRI dropped to 69% of baseline (Fig. 1). In the burn/LPS group, MAP showed a 14% decrease immediately after LPS infusion (Fig. 2). During the further post-LPS course, no significant differences were noticed between groups in MAP, CVP, Hct, or UP (Figs. 2 and 3).

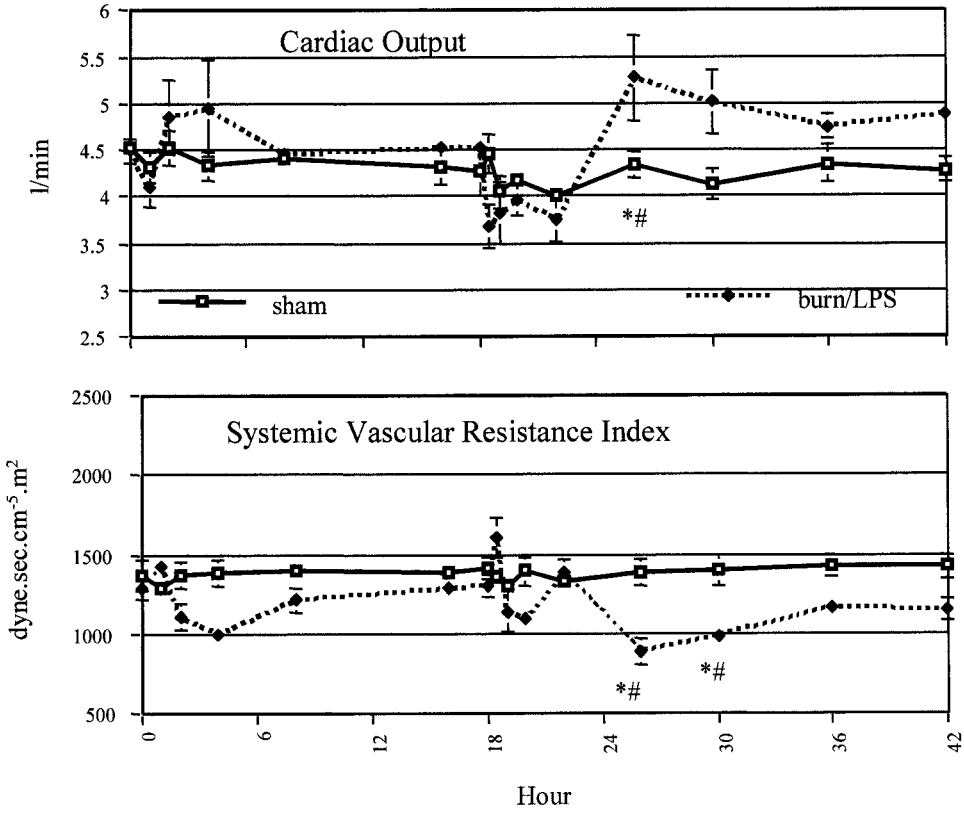

Fig. 1. *CO and SVRI after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

Hepatic Hemodynamics

Hepatic Arterial Circulation

In contrast to the CO, which remained within baseline range, Qh decreased significantly to approximately 52% of baseline level during the first 4 hours after burn (Fig. 4). This fall in Qh was associated with a significant increase in hepatic arterial vascular resistance (HAVR), reaching 462% of baseline as early as 1 hour after burn (Fig. 5). Hepatic arterial hemodynamic measurements recovered completely in all animals to baseline values at 18 hours after burn (Figs. 4 and 5).

Administration of LPS to burned animals resulted in a biphasic response of hepatic ischemia and reperfusion. The second insult resulted in a significant hepatic arterial vasoconstriction, with a 16-fold increase of HAVR during the first hour after LPS (Fig. 5). HAVR remained significantly increased (550% of baseline) for a period of 6 hours after LPS administration (Fig. 5). Correspondingly, Qh decreased significantly to 12% of baseline during the same time of maximum increase of HAVR (Fig. 4). After an initial recovery of Qh to baseline values 6 hours after LPS, a marked elevation (127–152% of baseline) was noticed during the following 6 hours (Fig. 4).

Hepatic Portal Circulation

During the first 4 hours after burn, Qp increased to approximately 132% of baseline (Fig. 6). Although no important changes were observed in the pattern of measured PVP, HPVR showed a 34% decrease of baseline values during the same time period (Figs. 7 and 8). Similar to the hepatic hemodynamic arterial variables, portal hemodynamic measurements showed the same pattern of recovery to baseline values at 18 hours after burn in all animals (Figs. 6, 7, and 8).

The second insult yielded significant alterations in the portal circulation, lasting for a prolonged time period. The HPVR showed a 2- to 4-fold increase during the first 8 hours after LPS administration (Fig. 7). During this early septic phase, a significant portal hypertension was noticed, whereas measured PVP was elevated to approximately 225% of baseline values (Fig. 8). Qp showed a biphasic response after LPS administration. During the first 8 hours after LPS, Qp decreased to approximately 51% of baseline (Fig. 6). After a transient recovery to baseline, a hyperdynamic phase with an elevation of Qp to 147% of baseline began at 30 hours (12 hours after LPS) and remained till the end of the study period (Fig. 6). During this late septic period, HPVR was decreased to 63% of baseline and PVP was slightly increased to 121% of baseline (Figs. 7 and 8).

Systemic Oxygen Delivery and Consumption

After a transient reduction, Do_2 and Vo_2 showed a marked increase during the first 6 hours after burn (Fig. 9).

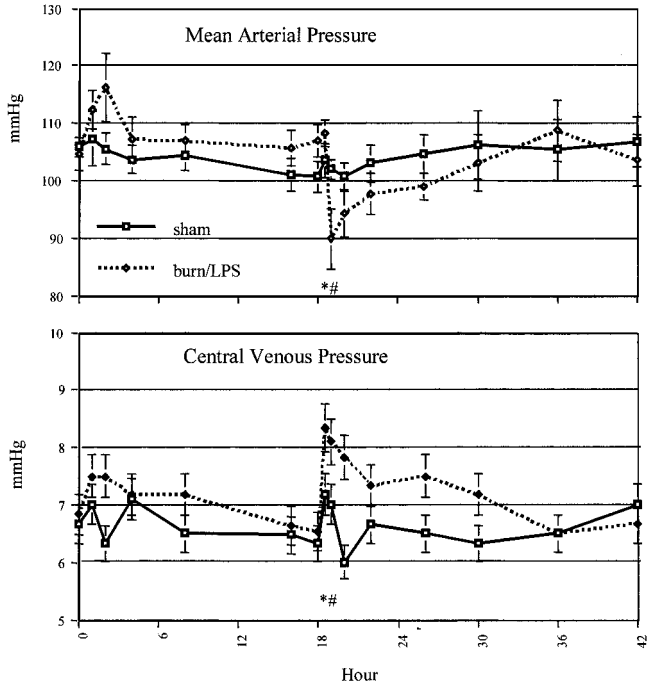

Fig. 2. *MAP and CVP after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

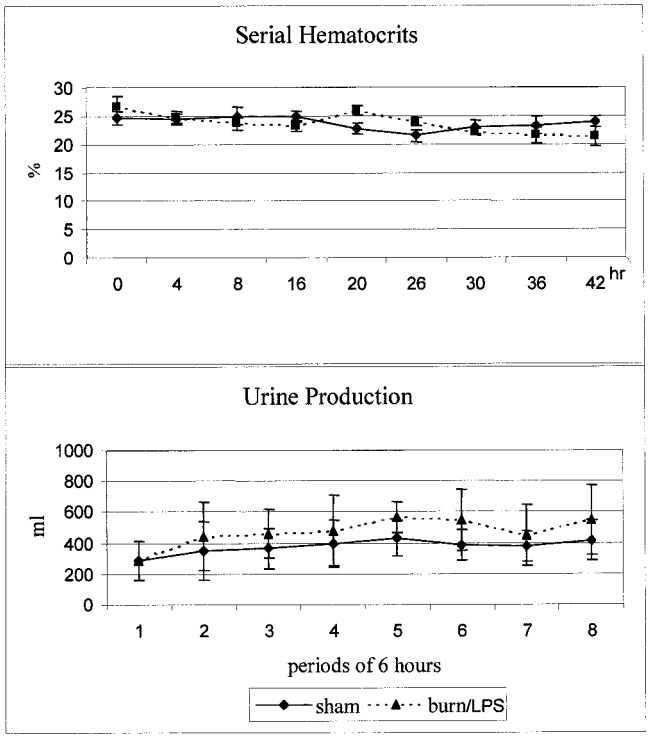

Fig. 3. *Hct and UP after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). No statistically significant differences were measured.*

Administration of LPS resulted in a significant drop in Do_2 during the first hour. Vo_2 was moderately decreased at this time point (Fig. 9). During the post-LPS hyperdynamic phase, both Do_2 and Vo_2 were increased.

Hepatic Oxygen Delivery and Consumption

hDo_2 was significantly reduced to 63% of baseline during the first 2 hours after burn. In contrast, hVo_2 was sustained within baseline values with a slight decrease of 16%, implicating increased hepatic oxygen extraction capacities during the postburn phase (Fig. 10).

As a result of the second insult (LPS administration), hDo_2 decreased significantly to 12% of baseline during the first hour after LPS and remained as low as 56% of baseline at 4 hours after LPS administration (Fig. 10). hVo_2 showed a similar pattern, whereas a significant decrease of 21 to 65% of baseline values was calculated during the first 4 hours after LPS (Fig. 10). After a transient increase in both oxygen delivery and consumption rates at 6 hours after LPS, a recovery to baseline range was reached at 36 hours (18 hours after LPS).

DISCUSSION

Burn injuries have been documented to have a negative impact on hepatic perfusion. The influence of severe thermal injury on hepatic blood flow was investigated in a 50% TBSA burn rat model, by using the tricarbocyanine dye indocyanine green.[9] Hepatic blood flow was decreased significantly by 0.5 hour after burn and remained approximately 20% below normal for 24 hours. The intrinsic efficiency of the liver in removing the indocyanine green dye from the systemic circulation was also reduced.

In an ovine model, the effect of 40% TBSA third-degree burn on effective liver blood flow was determined, by using the galactose infusion technique.[10] The effective liver blood flow was decreased by 50% in the first 5 hours after burn, even when the animals were resuscitated to baseline cardiac output values.

In our model, Qh showed a transient but significant decrease (48% of baseline) shortly after burn, which was associated with a 4.6-fold increase in HAVR. The measuring of a moderate increase in CO, at the same time period, suggests a selective vasoconstrictive impact of thermal trauma on the hepatic arterial circulation.

The second insult (LPS) yielded a dramatic and prolonged increase in HAVR (16-fold vs. baseline), which was associated with a significant reduction of Qh during the first 4 hours after endotoxin (12%–67% of baseline). After recovery to baseline, a reperfusion episode followed with an elevation of Qh to 152% of baseline values at 8 hours after endotoxin.

The impact of endotoxin on Qh, as observed in this study, is more pronounced compared with the results of a previous study.[11] The effect of endotoxemia on the hepatic circulation was evaluated in chronically instrumented and sedated sheep receiving a continuous intravenous infusion of

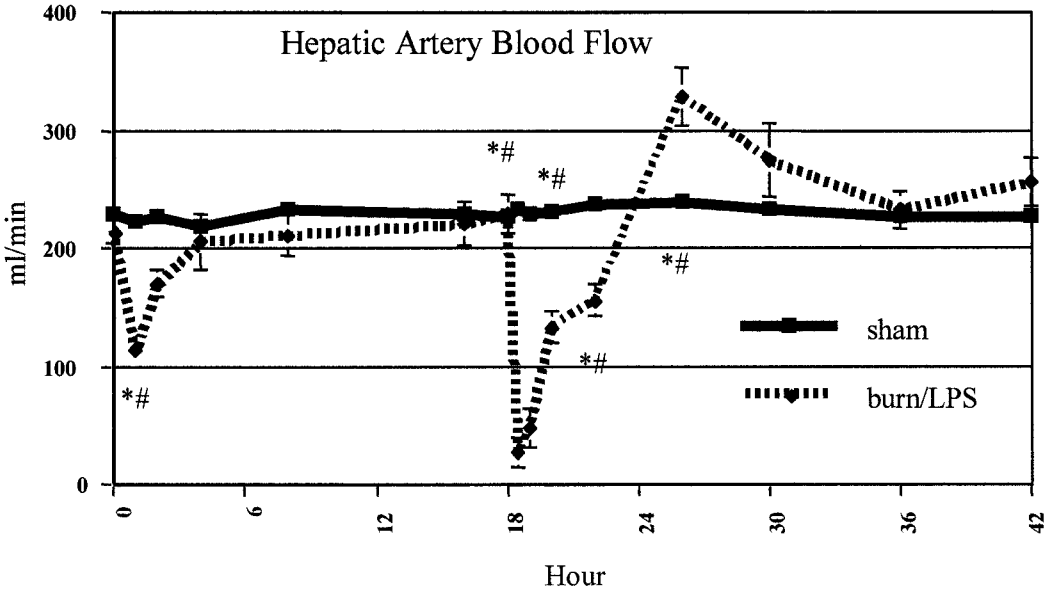

Fig. 4. *Qh after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

E. coli endotoxin.[11] The response of the hepatic artery was biphasic and consisted of a transient vasoconstriction followed by a transitory increase of Qh, reaching a maximum of 921% of baseline values after approximately 2 hours. The noticed dissimilarity might be due to the fact that different species and administration schemes were used. However, it is more likely that the priming impact of the early burn injury was responsible for the amplification of Qh response to endotoxin.

Under physiologic conditions, the regulation of Qh tends to buffer the impact of Qp changes on total hepatic blood flow to maintain the latter constant. The function of Qp as the major intrinsic regulator of hepatic arterial tone is known as the hepatic arterial buffer response.[12] This buffer function seems to depend on portal blood flow washing away local concentrations of adenosine from the area of arterial resistance.[13] Thus, a reduction in portal blood flow causes an increase in local adenosine levels, resulting in arterial

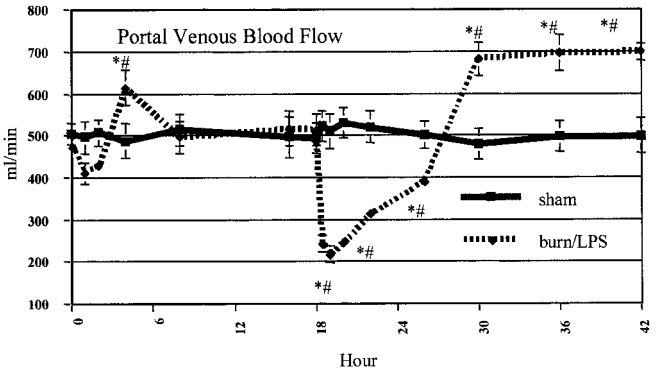

Fig. 6. *Qp after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

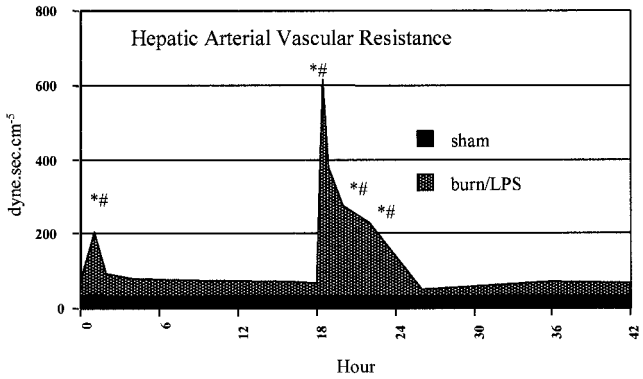

Fig. 5. *HAVR after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

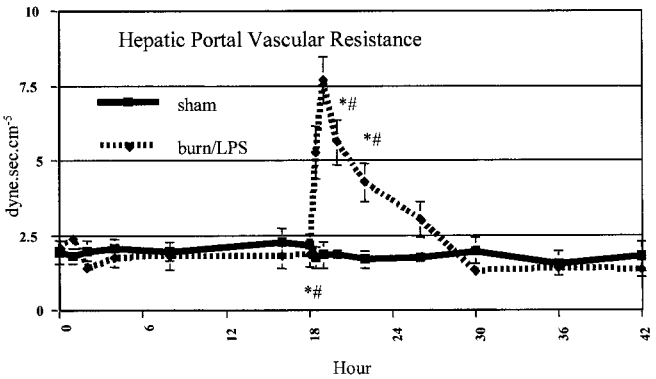

Fig. 7. *HPVR after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

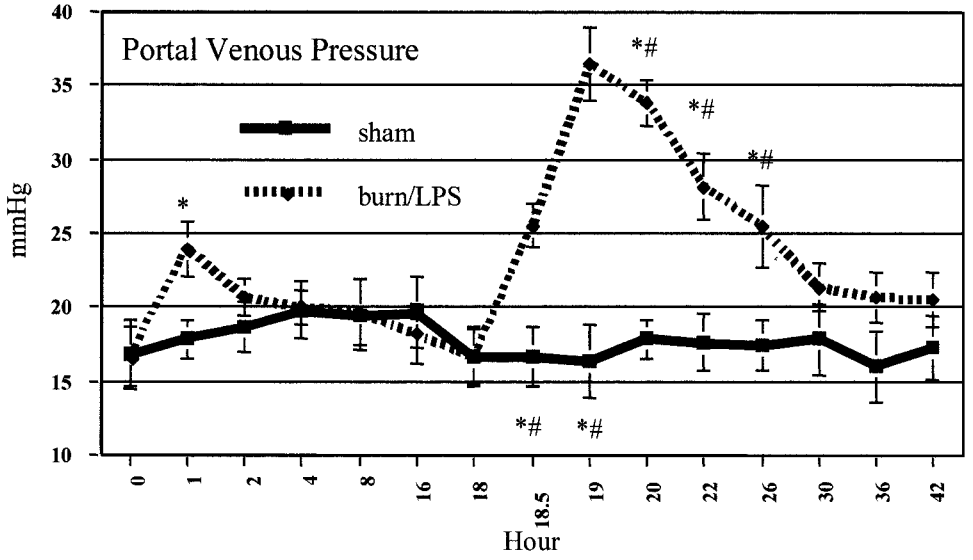

Fig. 8. *PVP after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

dilation.[13] Because the Qp is determined by the vascular resistance of the intestine and, to a lesser extent, the spleen and pancreas, a decrease in the mesenteric blood flow would result in a compensatory increase in hepatic blood flow to maintain liver function.

In contrast with this scenario, in our model of postburn endotoxemia, the response of the Qh was unrelated to changes in portal circulation. An early postburn transient hepatic vasoconstriction was found to occur before changes in portal circulation (1 hour vs. 2 hours after burn), demonstrating the relative independence of hepatic arterial response in relation with other splanchnic blood flow. This ischemic insult may explain the occurrence of transient hepatic function disorders, commonly seen early after burn and may also adversely influence the phagocytic capacities of hepatic macrophages. It is also possible that this hepatic ischemic insult

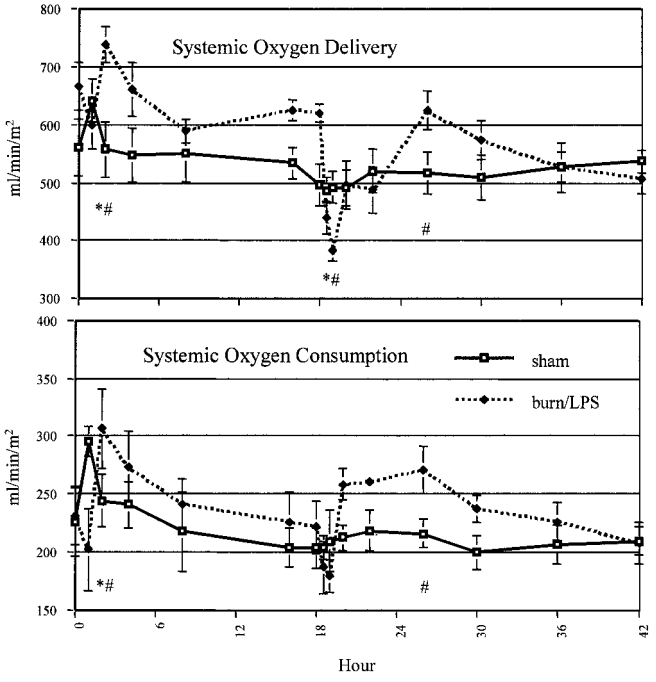

Fig. 9. *Do_2 and Vo_2 after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

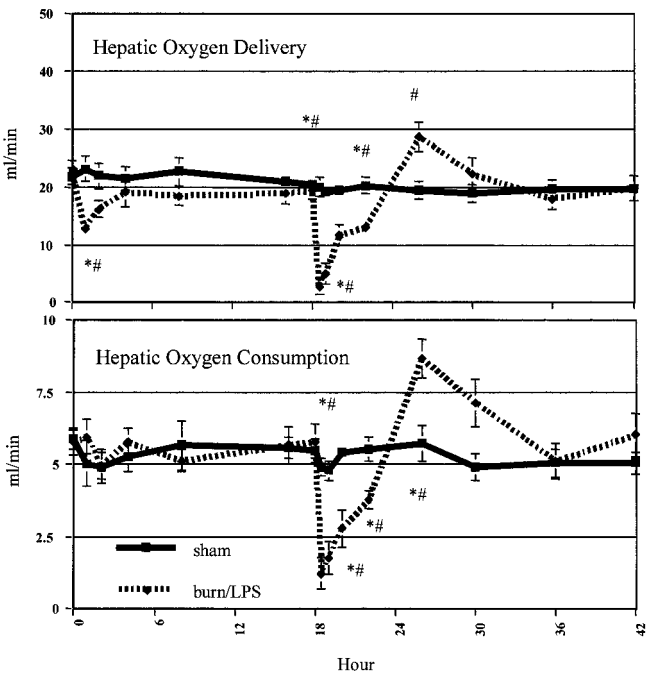

Fig. 10. *hDo_2 and hVo_2 after 40% TBSA third-degree burn (0 hour) and endotoxin (*E. coli *LPS,18 hours after burn). Values are $p < 0.05$: asterisks, versus baseline; pound signs, versus sham.*

may prime hepatic macrophages, leading to release of certain vasomediators, such as thromboxanes, which have been implicated in the pathophysiologic mechanism of postburn mesenteric vasoconstriction.[14] Despite the marked reduction in Qp during the first 8 hours after endotoxin, Qh showed a significant decrease for a period of 4 hours, indicating a loss of the hepatic arterial buffer response. The magnitude of the hepatic response after the second insult may demonstrate the priming effect of the first insult. In an intact porcine model of endotoxemia, Ayuse et al. have observed a similar alteration in the hepatic arterial buffer response.[15] It has been suggested that certain mediators, gut derived or generated by presinusoidal Kupffer cells, are implicated in the pathophysiologic process of the impaired hepatic arterial buffer response.[11] Another possible mediator could be nitric oxide (NO), because it has been reported to be involved in the pathophysiology of liver injury during ischemia/reperfusion and endotoxemia.[16–18] It has been suggested that endogenous NO formation is sufficient to limit ischemic liver injury during reperfusion and that inhibition of NO synthesis will result in additional ischemic damage.[16] NO has been reported to modulate hepatic arterial but not portal venous resistances under baseline conditions, induce hepatic arterial vasodilation, and attenuate the increase in portal resistance during endotoxic shock.[17] Another experimental study has demonstrated that inhibition of eNOS (L-NAME) has a detrimental effect on liver injury during ischemia/reperfusion and endotoxemia, mainly because it can cause additional ischemia by reducing the microvascular blood flow.[18]

The marked portal hypertension, seen in the postburn endotoxemic period, may account for the occurrence of bacterial translocation and contribute to the previously reported phenomenon of endotoxin induced bacterial translocation.[19] Acute portal hypertension has been previously shown to promote bacterial translocation.[20] The underlying mechanisms are probably the disruption of the intestinal mucosal barrier caused by acute venous congestion, increasing splanchnic blood pooling, edema, and ischemia.[15,21] Portal hypertension initiated by endotoxin has also been shown to induce hepatic microcirculatory disturbance, which may cause liver injury.[22]

It is well known that oxygen delivery and utilization is deranged in the setting of sepsis. Patients with septic shock require higher levels of Do_2 to maintain aerobic metabolism. When Do_2 is inadequate, peripheral tissues switch to anaerobic metabolism and Vo_2 decreases.[23] The most likely cause is an inability of the microvasculature to provide sufficient oxygen to actively metabolic tissue, probably as a result of diminished autoregulatory control and capillary damage.[24]

In our study, systemic Do_2 and Vo_2 showed a similar pattern of increasing, as seen in CO after thermal injury. On the contrary, hDo_2 was significantly reduced during this early postburn phase. At the same time, hVo_2 did not show any significant changes, as evidence of an increased oxygen extraction capacity of hepatic cells. It is well known that the liver can extract nearly 100% of the available oxygen.[25] This process seems to be the primary compensatory adjustment after a reduced hDo_2.

The impact of this second insult on the hepatic oxygenation was dramatic. A pathologic flow-dependent hVo_2 response was observed, with a pronounced and prolonged hypoxic period. The first 4 hours after LPS administration to burned animals were marked with a significant decrease in hDo_2. Hepatic oxygen consumption showed a pathologic hDo_2 dependency, leading to an oxygen debt that limits metabolism. This early decreased hVo_2 indicates the inability of the liver to compensate inadequate oxygen delivery by increasing oxygen extraction, resulting in tissue hypoxia. These results could be explained by a defect in microvascular regulation of blood flow that interfered with the optimal distribution of a limited Do_2 in accordance with tissue oxygen needs.[26] The development of flow-dependent liver hypoxia was shown before in a septic shock pig model and was reflected in a decrease in liver lactate turnover (increased liver lactate release) during late sepsis.[27] Early hypoxia in the splanchnic region is suggested as a plausible mechanism behind the development of secondary organ failure, especially in sepsis.[27] Recently, nitric oxide has been shown to be involved in hepatic oxygen transport and consumption during endotoxemia.[28,29] The role of nitric oxide in hepatic oxygen transport is unclear. In a porcine model of endotoxemia, NO was found to ameliorate deterioration of hepatic oxygen transport and liver function induced by endotoxin.[29] In another study, selective inhibition of iNOS activity was found to restore Qh and increase hVo_2 in pigs with endotoxemia.[28]

In conclusion, thermal injury seems to induce a selective vasoconstrictive effect on the hepatic arterial circulation, yielding hepatic ischemia and a reduction of hepatic oxygen delivery. The magnitude of the hepatic response to a second insult (endotoxemia) is magnified and manifested as a pronounced hepatic ischemia/reperfusion episode, associated with an inadequate hepatic oxygen delivery and a pathologic supply dependent hepatic oxygen consumption. A loss of the hepatic arterial buffer response, as indicated by a profound decline in both portal venous and hepatic arterial blood flow, seems to be one of the mechanisms responsible for this phenomena. In addition, postburn endotoxemia seems to induce severe portal hypertension, which may contribute to gut barrier dysfunction after thermal injuries.

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