

## EFFECTS OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITOR ENALAPRIL ON BACTERIAL TRANSLOCATION AFTER THERMAL INJURY AND BACTERIAL CHALLENGE

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**ABSTRACT**—Burn injury and sepsis produce acute gastrointestinal derangements that may predispose patients to bacterial translocation. We studied the effects of enalapril, an angiotensin converting enzyme inhibitor (ACEi), on gastrointestinal anatomic alterations, bacterial translocation, and related mortality during gut-derived sepsis in burned mice that had received a prior bacterial challenge. BALB/c mice (n = 111) were treated with enalapril 10 or 1 mg/Kg body weight or sterile saline as control twice daily for 3 days. They were then gavaged with  $10^9$   $^{111}\text{In}$  radiolabeled or unlabeled *Escherichia coli* and given a 20% total body surface area (TBSA) burn injury. Animals gavaged with unlabeled bacteria were observed for survival (n = 60). Survival was significantly higher in the group receiving enalapril 10 mg/Kg compared with control (75% vs. 10%). Mice treated with enalapril maintained small intestine weight, measured 4 h postburn, and ileal mucosal height was preserved, whereas burned untreated animals lost intestinal weight and mucosal height. Bacterial translocation was decreased in mice treated with enalapril, but killing was unaffected. This study suggests that treatment with enalapril positively affects the outcome in gut-derived sepsis by ameliorating gastrointestinal structural and functional damage and decreasing bacterial translocation.

### INTRODUCTION

Microbial translocation is defined as the passage of both viable and nonviable microbes as well as their products across the intact intestinal mucosal barrier. Translocation has been shown to be important in the hypermetabolic response to burn injury (1), and many investigators feel it is important in the genesis of multisystem organ failure (2–4). Recent studies have suggested that intestinal ischemia occurring as a consequence of acute injury may play a role in the pathophysiology of gut barrier failure and subsequent bacterial translocation (5, 6). Using a variety of experimental models in which reduction of intestinal blood flow is a prominent feature, the incidence of bacterial translocation is diminished by different therapeutic agents that affect the microcirculation. Recently, our group showed that treatment with heparan sulphate, an acid polysaccharide with antithrombogenic properties, was able to decrease bacterial translocation and improve the outcome after thermal injury, probably by improving the microcirculation (7). Another study, using ultrasonic flow probes, showed that mesenteric blood flow decreased acutely after thermal injury in sheep (8), and maintenance of intestinal blood flow through mesenteric arterial infusion of a vasodilator resulted in a lowered incidence of bacterial translocation to the MLN and viscera (9). Acute thermal injury may produce a relative state of hypovo-

lemia, resulting in activation of the renin-angiotensin system with subsequent splanchnic vasoconstriction.

The purpose of this study was to assess the effect of enalapril, an angiotensin converting enzyme inhibitor, on bacterial translocation, related mortality and intestinal anatomy during gut-derived sepsis in burned mice.

### MATERIALS AND METHODS

#### *Animals and animal care*

Adult female BALB/c mice (H-2<sup>d</sup>) (Charles River Laboratories, Wilmington, MA) weighing between 18 and 22 g, were used in this study. They were caged in groups of five with food (Rodent Laboratories Chow 5001, Purina Mills, Inc., St. Louis, MO) and water ad libitum, with a 12 h light/dark cycle, during a quarantine period of 1 wk so they could adapt to the standard laboratory environment and to exclude any underlying diseases. The protocol was approved by the University of Cincinnati Medical Center's Institutional Animal Care and Use Committee, and the animals were housed in a facility approved by the American Association for the Accreditation of Laboratory Animal Care. All investigations adhered to the *Guide for the Care and Use of Laboratory Animals* as set forth by the Committee on the Care and Use of Laboratory Animals, National Research Council of the United States Department of Health and Human Services and National Institutes of Health.

#### *Preparation of enalapril and treatment of the animals*

Angiotensin converting enzyme (ACE) inhibition was induced by treatment with a suspension of enalapril maleate (Vasotec, Merck Co., West Point, PA) at a concentration of 1.25 mg/mL. The drug was supplied in solution and stored at room temperature. It was diluted to the desired concentration immediately before use in sterile phosphate buffered saline (PBS, pH 7.4).

At the time of treatment, animals received enalapril in 0.2 mL PBS injected subcutaneously (s.c.) in the nape of the neck. The doses used were selected from the literature to provide a high and low response. An equal volume of sterile PBS was given to the control group.

#### *Preparation of $^{111}\text{In}$ labeled E. coli*

*Escherichia coli* (Stock #53104, University of Minnesota, Minneapolis, MN) was inoculated in 25 mL brain heart infusion broth (Baltimore Biological

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Laboratories, Baltimore, MD) and incubated overnight at 37°C in a shaking incubator. This culture was centrifuged at 4000 rpm for 10 min and washed twice in sterile saline solution. The pellet was resuspended in sterile saline and 1 mCi of  $^{111}\text{In}$  oxine (Syncor, Cincinnati, OH) was added and then incubated for 40 min at 37°C. The isotope-labeled bacteria were washed, resuspended in sterile saline solution, and adjusted to a final concentration of  $1 \times 10^9$  microorganisms/0.2 mL using a Klett densitometer (Klett Manufacturing Co., Long Island, NY). Viable organism counts were verified by dilution and enumeration of colony forming units (CFU). Prior experiments showed that once cell associated, the label was stable with <5% dissociation over 4 h incubation of the bacteria in saline at 37°C. Loss of label occurs with death of the bacteria.

### Gavage and burn procedure

One day before burn injury, the hair of animals' torsos was removed by clipping. Food was withheld for 18 h, but water was provided ad libitum before gavage with 0.2 of  $^{111}\text{In}$  *E. coli* while the animals were awake. After gavage, they were anesthetized with methoxyflurane inhalation, and a 20% full-thickness flame burn was inflicted using the technique of Steritz and Holder (10). Saline 0.2 mL was given intraperitoneally immediately after burn injury for fluid resuscitation, and the animals were allowed to recover from anesthesia with free access to food and water.

### Statistical analysis

To achieve a normal distribution of the data, the dpm values were converted to a logarithmic scale ( $\log_e$ ). Statistical analysis for radionuclide counts, the number of CFU, and the percentage of viable bacteria was performed with the analysis of variance (ANOVA) technique followed by Tukey's test. Survival rates were analyzed by Chi-square test. The difference among the means was considered significant if the *p* value was  $\leq .05$ .

### Experimental design

All of the following experiments were repeated two times or more, and the results present data pooled from replicated studies.

**Experiment I**—Sixty animals were used for the mortality study. The BALB/c mice were randomized into three groups ( $n = 20/\text{group}$ ) to receive 1) enalapril (10 mg/Kg; enalapril-10); 2) enalapril (1 mg/Kg; enalapril-1); or 3) an equal volume of sterile PBS (control) every 12 h for 3 days. Then the animals were gavaged with  $10^9$  *E. coli* followed immediately by a 20% thermal injury. Survival was observed for 10 days postburn.

**Experiment II**—An additional 30 animals underwent the same procedures described in Experiment I, except they were gavaged with  $10^9$   $^{111}\text{In}$  radiolabeled *E. coli* in 0.2 mL and killed 4 h after burn. This time was selected based on previous experiments that showed 4 h to be the peak time of bacterial translocation from the gut following burn injury (11). Then the animals' abdomens were prepared with 70% alcohol, and by a midline laparotomy, mesenteric lymph nodes (MLNs), spleen, and liver were harvested using aseptic techniques. The solid tissues were weighed individually and homogenized after the addition of 1.0 mL of sterile normal saline. One hundred microliters of the homogenate was removed and plated on eosin methylene blue (EMB) plates (Becton and Dickinson, Cockeysville, MD) for quantitative colony counts after 18 h of aerobic incubation at 37°C. The number of CFUs per gram of tissues was determined by multiplying the actual counts by  $1 + \text{weight} \times 10/\text{weight}$ . To ensure that *E. coli* grown from the tested tissues was the same species as the gavaged *E. coli*, the Sceptor System Test #80401 (Becton Dickinson, Towson, MD) was used. The system employs a combination of antimicrobial susceptibility tests, biochemical identification, and a  $\beta$ -lactamase test to identify specific species of enteric bacteria.

The remaining portion of homogenates was used to determine radionuclide counts (as measured by degradation per minute; dpm). The counts were determined using a  $\gamma$  counting system (Beckman Model Gamma 5500, Beckman Instruments Inc., Fullerton, CA). The radioactivity in tissues was expressed as dpm/g of tissues. We determined that one dpm count corresponded to approximately eight viable bacteria (this value was obtained by counting the radionuclide and viable bacterial counts in serial dilutions of the gavaged suspension) as measured by a Klett densitometer.

The percentage of bacteria that remained alive in tissues was calculated by the following formula:

$$\frac{\text{CFU/g}}{\text{dpm/g} \times 8} \times 100$$

**Experiment III**—Twenty-one BALB/c mice were used for anatomical and histology studies. The mice were randomized into three groups ( $n = 7/\text{group}$ ) to receive 1) enalapril (10 mg/Kg; enalapril-10); 2) enalapril (1 mg/Kg; enalapril-1); or 3) an equal volume of sterile PBS (control) every 12 h for 3 days. Then the animals were gavaged with  $10^7$  *E. coli* followed immediately by a 20% thermal injury. The low dose of *E. coli* was used to prevent mortality. At 24 h postburn, animals were killed and the intestine was removed for anatomical and tissue analysis. The small intestine was removed, carefully dissected away from the mesentery, and a 10 cm segment of proximal jejunum taken from 5 cm beyond the pyloroduodenal junction as well as a 10 cm segment of ileum taken from the middle part of the small intestine. Then the lumen was emptied and washed, and the specimen weighed.

At the time of killing, samples from the ileum of seven animals/group were excised and immersed in a fixative composed of 2% glutaraldehyde and 2% paraformaldehyde in .1 M sodium cacodylate buffer (pH 7.4). The segments were held in the fixative at 4°C until further processing. After a wash in sodium cacodylate buffer, the specimens were fixed in a 1% osmium tetroxide, dehydrated into absolute ethanol and embedded in Epon-Araldite resin. A Reichart ultra microtome (Leica Inc., Deerfield, IL) was used to cut sections at 1–2 microns ( $\mu\text{m}$ ). The slides were stained with hematoxylin and eosin. Tissue samples were examined blindly for histologic features. Intestinal villous height was measured in microns from the tips of the villi to the base of the submucosa, using a micrometer incorporated in the microscope with Semicaps digital acquisition system and a Sony Model XC-37 CLD camera. Multiple measurements were made of each section and values averaged to obtain a mean value for mucosa thickness for each group.

## RESULTS

### Experiment I: Survival after burn and gavage

Enalapril administration was well tolerated by all the animals. In this model, the survival rate, after 10 days, was 75% (15/20) for the animals treated with enalapril-10, 40% (8/20) for animals treated with enalapril-1, and 10% (2/20) for control group. All animals that died did so within 48 h. The group treated with enalapril-10 showed a highly significant improvement in survival rate compared to nontreated animals ( $p < .0001$ ). Enalapril-10 treated animals also showed a better survival compared to enalapril-1, but this difference was not significant (Fig. 1).

### Experiment II: Study of translocation and bacterial survival

The magnitude of translocation of  $^{111}\text{In}$  *E. coli*, as measured by dpm/g of tissue for the three groups is shown in Fig. 2. Nontreated animals had a greater amount of bacteria translocating to the MLNs, liver, and spleen compared with animals treated with enalapril-10. This difference was significant in the liver and spleen ( $p < .05$ ). Animals treated with enalapril-1 also had a significantly lower amount of translocation to the liver compared to control animals ( $p < .05$ ).

The analysis of the number of viable *E. coli* (as measured by CFU/g tissue) recovered from the tissue showed that mice treated with enalapril had fewer viable bacteria in the MLN and spleen compared with the control group, but this difference was not significant (Fig. 3).

The calculated percentage of translocated bacteria that survived showed no statistical differences among the three groups (Fig. 4).

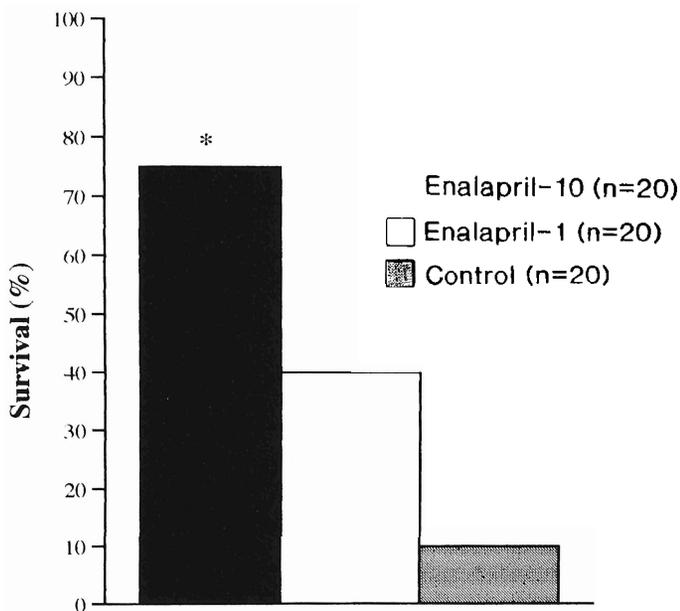


FIG. 1. Survival of mice gavaged with  $10^9$  *E. coli* and then given a 20% thermal burn. Enalapril-10 = animals treated with enalapril 10 mg/Kg twice daily for 3 days before burn; Enalapril-1 = animals treated with enalapril 1 mg/Kg twice daily for 3 days before burn; Controls received saline injections. \* $p < .05$  compared with control.

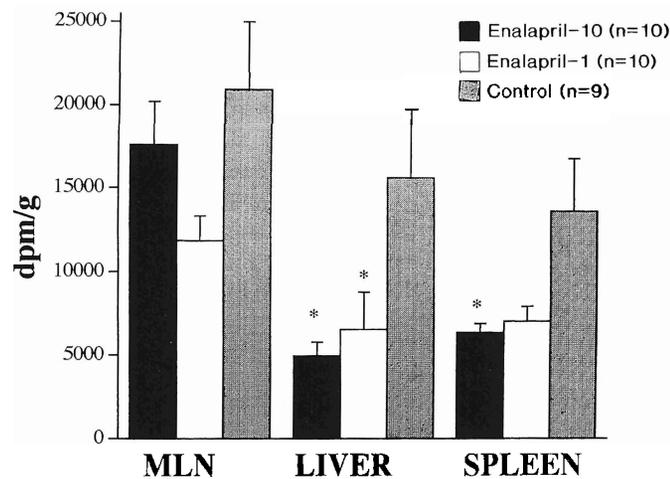


FIG. 2. Translocation to the mesenteric lymph nodes (MLN), liver, and spleen as measured by radionuclide concentration (dpm/g of tissue) 4 h after burn and gavage. Treatment groups are as defined in Fig. 1. \* $p < .05$  compared to control. Values are mean  $\pm$  SEM.

**Experiment III: Effect of enalapril on small intestine weight and structure**

In burned and gavaged animals treated with enalapril, the intestinal weight was significantly greater compared to the control group. Animals treated with enalapril-10 showed a higher jejunal and ileal wet weight compared to nontreated animals ( $p < .001$  and  $p < .05$  respectively, Table I). Moreover, enalapril-1 animals showed a significantly higher ileum wet weight compared with the control group ( $p < 0.001$ , Table 1).

Measurement of distal ileum thickness by microscopic examination showed that mucosal thickness was significantly increased in burned mice treated with enalapril compared with

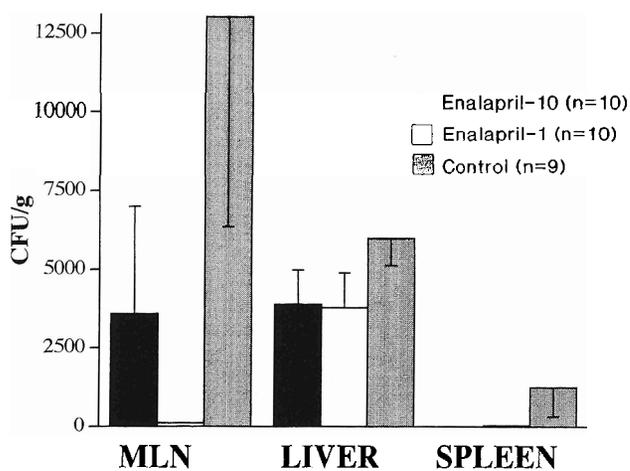


FIG. 3. Numbers of viable bacteria recovered from MLN, liver, and spleen 4 h after burn and gavage in the treatment groups and controls. Values are mean  $\pm$  SEM.

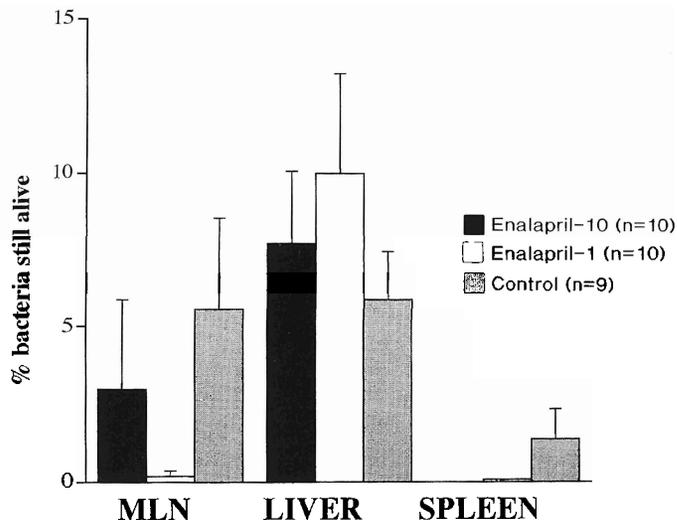


FIG. 4. Calculated percentage of bacteria that survived in the tissues 4 h after burn and gavage in the treatment groups and controls. Values are mean  $\pm$  SEM.

the burn-untreated group ( $p < .05$ ). Moreover, the enalapril-10 group showed better preservation of mucosal thickness compared to enalapril-1 animals ( $p < .05$ , Table 1).

In the burned-untreated control mice, marked destruction and fragmentation of the villi were evident, as well as vacuolar degeneration. In the treated groups, destruction and fragmentation of villi were less pronounced, and vacuolar degeneration was less pronounced.

**DISCUSSION**

Despite multimodal therapy, improved intensive care techniques, and preoperative support, septic shock and MOF continue to be important sources of morbidity and mortality in the critical care setting. During severe injury, metabolic demand of the gastrointestinal (GI) tract for oxygen may exceed delivery, resulting in a relative mucosal ischemia (12). Optimal blood and oxygen supply to the GI tract may be one of the key factors for maintaining physiologic barrier function. In the presence of inadequate blood flow and/or inadequate oxygenation, the in-

TABLE 1. Effect of enalapril on intestinal weight and height 24 h after gavage with  $10^7$  *E. coli* and 20% TBSA thermal injury

Group	No. of Mice	Intestinal Weight (mg/cm)		Mucosal Height ( $\mu$ m) (Mean $\pm$ SEM)	No. of Observations
		Jejunum	Ileum		
Enalapril-10	7	24.4 $\pm$ 1.2*	18.9 $\pm$ 1.3 <sup>‡</sup>	380.1 $\pm$ 3.6 <sup>‡§</sup>	126
Enalapril-1	7	21.9 $\pm$ 1.3*	16.6 $\pm$ 1.4	287.6 $\pm$ 3.2	134
Control	7	12.0 $\pm$ 0.3	13.1 $\pm$ 1.1	161.8 $\pm$ 5.4	223

\* $p < .001$  vs. Control; <sup>‡</sup> $p < .05$  vs. control; <sup>§</sup> $p < .05$  vs. enalapril-1.

testine may lose the capacity to contain microorganisms and toxic products that are in the lumen. Recent studies showed that splanchnic ischemia allows bacteria and endotoxin to cross the gut wall and invade local MLN or even the blood stream, leading to septic shock and MOF (2, 13). Subsequent mucosal dysfunction has been implicated in the pathology of ongoing sepsis through translocation of enteric bacteria or their products into the systemic circulation.

Thermal injury has been shown to alter the splanchnic blood flow. Omental and mesenteric vasoconstriction have been described following burn injury, and this phenomenon appeared to be proportional to the size of burn (14, 15). Several studies showed that burn trauma greatly reduced the intestinal blood flow, and consequent splanchnic vasoconstriction and tissue ischemia were directly correlated with a remarkable enhancement of bacterial translocation (16–19). Jones et al. observed a decrease in small bowel blood flow by 4 h after 30% dorsal scald burn in a small animal model. The decrement in blood flow occurred despite an increased cardiac index (20). Morris and coworkers have also documented a significant decrease in blood flow through the superior mesenteric artery using ultrasonic flow probes in large animals subjected to a 30% burn injury (18). They further demonstrated that after burn injury, the infusion of the vasodilator nitroprusside resulted in maintenance of mesenteric blood flow and was associated with diminished incidence of enteric organisms translocating to the MLNs and abdominal viscera.

Thermal injury results in losses of intravascular volume due largely to sequestration of fluid within injured tissues. It may be postulated that the relative hypovolemia resulting from postburn sequestration may lead to activation of the renin-angiotensin system that produces elevated circulating levels of angiotensin II (ANG II). Endogenous ANG II appears to exert a profound and primary influence on mesenteric blood flow (21, 22). Classically, ANG II has been viewed as a plasma hormone. The discovery of components of the renin-angiotensin system in many tissues of the body has led to the hypothesis that, in addition to being a plasma hormone, ANG II may be formed locally, and therefore possess an additional paracrine action, participating in the regulation of local vascular tone. All components of the renin-angiotensin system are present within the intestine, and production of ANG II does occur locally within this tissue. For example, both renin substrate and renin have been shown to exist with the wall of splanchnic arteries (23). ACE is also localized within the endothelial lining of mesenteric vessels (24). Thus, ANG I entering the mesenteric vasculature or locally formed can be rapidly hydrolyzed to ANG II.

Stimulation of the renin-angiotensin system results in ANG

II formation, which leads to vasoconstriction, sodium retention, and increased blood pressure (25). ACEi act by interfering with the conversion of ANG I to active ANG II, thereby preventing vasoconstriction and decreasing the blood pressure. The key to the action of ACEi on the renin-angiotensin system is their affinity for zinc ion binding site on ACE. Enalapril binds to the zinc binding site via a carboxylic group.

Gasic et al. observed that in humans an ACEi counteracted ANG I-dependent changes in the splanchnic circulation, with both arterial and venous effects (26). Moreover, several studies suggest that under physiological circumstance the renin-angiotensin system plays a minor regulating role in the splanchnic vascular bed but gain great pathophysiological importance in conditions of compromised hemodynamic function (27, 28).

In a recent study, Buyukgebiz et al. showed that an ACEi exerted a significant protective effect on the intestinal mucosa after mesenteric ischemia-reperfusion injury (29). They demonstrated that this protection was accomplished by increased endothelin release after injury. Endothelin belongs to a vasoactive peptide family consisting of three isopeptides that interact with two different receptors that have distinct cell type/tissue distributions with different physiological effects (30). Endothelin A receptors are generally in smooth muscle cells and mediate vasoconstrictor responses, whereas the endothelial cells that express endothelin B receptors mediate vasodilator effects via the endothelin-induced release of nitric oxide (30).

The intestinal mucosa serves as an important mechanical barrier that prevents bacteria and their products from reaching the mesenteric lymph nodes and internal organs. Burn injury induces alterations in both major components of the GI tract barrier: the epithelial cell layer (1) and humoral-mediated and cell mediated immunity (31). Although the immune depression that accompanies severe burn injury may facilitate bacterial translocation, structural abnormalities of the GI mucosa may also alter the mechanical barrier to translocation. After thermal injury, splanchnic ischemia results in decreased small intestine mucosal weight, altered small intestine transport of nutrients, and decreased DNA synthesis in GI mucosal cells (32).

We found enalapril treatment decreased the incidence of bacterial translocation in burned mice. Small intestine wet weight and mucosal thickness were also preserved with enalapril treatment. Prior experiments have shown that bacterial gavage in burned animals did not affect gut morphology significantly (data not shown). These results are in agreement with a recent study by Jones et al. that showed that enalapril treatment resulted in maintenance of small bowel blood flow after thermal injury, and this was associated with a significantly reduced incidence of bacterial translocation to the MLN

(20). This reduction of bacterial translocation occurred despite increased counts of cecal Gram-negative aerobic bacteria.

To study the prevention of shock-induced translocation, Reed and associates used different models of fluid resuscitation (33). The most effective therapy appeared to be 3% hypertonic saline plus shed blood in a 1:1 ratio. They concluded that this was due to an adequate maintenance of gut microcirculation. This hypothesis found support in the data obtained from our laboratory showing that the magnitude of translocation of *Candida albicans* was inversely correlated to the microcirculatory flow within individual intestinal villi rather than alterations of the systemic blood pressure after thermal injury (34). Recently, our group showed that treatment with heparan sulphate, an acid polysaccharide with antithrombogenic properties was able to improve the outcome after thermal injury, decreasing bacterial translocation, probably by improving the microcirculation (7). In another study, our laboratory observed that administration of anti-interleukin-6 antibody was able to have a protective effect on the gut barrier function (35).

In summary, our data showed that enalapril treatment has a beneficial effect on the gut after burn injury and bacterial challenge, with a consequent increase in survival. This beneficial effect was related to an improved gut barrier function, probably due to a preserved gut microcirculation. Moreover, the animals treated with enalapril maintained small intestine weight and ileal mucosal height 24 h after injury.

In the clinical setting, ACEi therapy may have future use in the treatment of sepsis and other generalized inflammatory processes after severe injury. ACEi may improve or maintain visceral organ perfusion during bacteremia, possibly preventing tissue injury and influencing the development of multiple organ failure.

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