these processes in the reperfusion phase of hemorrhagic shock (5, 12). Dr. Mori and colleagues (4) have shown that the process has already started in the ischemic phase and so may be amenable to early modification. There is certainly rodent evidence that free radical scavengers reduce bacterial translocation (12) and the production of gut-derived inflammatory cytokines (13). However, is reducing lipid peroxidation in itself clinically significant? As the MRC CRASH trial of corticosteroids after significant head injury has shown, a treatment that, in principle, reduces lipid peroxidation may not translate into a clinically significant benefit (14).

Before the results of this interesting study have us reaching for the edaravone, there is a lot to learn. We need to know whether edaravone has any effect on the gut-derived inflammatory response in this model of hemorrhage. Although it has an effect when given at the start of ischemia, we need to know whether it has any effect when given during reperfusion/resuscitation. Clinically, that is when it is most likely to be used. Given that bacterial translocation is a relatively common phenomenon in rodent models, and well tolerated, it would be important to evaluate edaravone's effect in a large mammal model of hemorrhagic shock. It would also be important to know if edaravone has an effect on a clinically significant outcome, such as mortality, rather than just on surrogate outcomes, such as bacterial translocation or the generation of inflammatory mediators.

So, in answer to the original question: After the study by Dr. Mori and colleagues (4) we are better informed, but in terms of the management of grade IV hemorrhage in humans, we are still none the wiser.

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Bacterial translocation and intestinal neutrophil lipid peroxidation in a hemorrhagic shock model—Rat race or rat trap?*

"Trap 'em!" the ratman cried, disgusted. "You won't catch many rats that way! Rats isn't rabbits you know. . .Rats is clever, let me tell you that. If you want to catch 'em, you got to know 'em. You got to know rats on this job."—The Ratcatcher, by Roald Dahl

Bacterial translocation (BT) is the phenomenon of intestinal transmural passage of live bacteria and/or their cell wall components, such as liposaccharide or peptidoglycan polysaccharide. Many factors have been shown to predispose to BT—reduced splanchnic blood flow, intestinal mucosal damage, immunodeficiency, parenteral nutrition, antibiotic therapy, and bacterial overgrowth (1–4). The conduit for entry of these bacterial products and other nonbacterial soluble factors into the systemic circulation is the mesenteric lymphatics and not the portal vein (4–7). These products have been shown to exert distant and peripheral cytotoxic effects, for example, to endothelial cells and macrophages (5–9). It is the aggressive inflammatory incentive of these allegedly gut-derived villains that drives the argument for the central role that the gut plays in the pathogenesis of postinjury multiple organ failure (1, 3, 4, 8), hence the plethora of studies (mostly animal models) into bacterial translocation, splanchnic hypoperfusion, gut ischemia/reperfusion, gut-derived proinflammatory mediators, transcription factors, and so on. In order that the rat does not cast a cat among the pigeons, it is encouraging to know that these physiologic phenomena transcend species distinctions, being found in our cardiovascular and gastrointestinal physiologically similar porcine brethren as well (6).

*See also p. 1064.

Key Words: bacterial translocation; lipid peroxidation; free radical scavenger; hemorrhagic shock; ischemia/reperfusion

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The importance of reactive oxygen species/free radicals in mediating the activation of immune cells during shock and its resuscitation suggests that strategies aimed at reducing the oxidant load may be advantageous in modulating the inflammatory response. One of the main sources of free radicals and inflammatory cytokines during global ischemia-reperfusion is the gut (5, 8, 9). These free radicals generated during reperfusion after ischemia are proposed to be the marauding assailants of endothelial cells (5, 9), and therefore free radical scavengers would police this threat.

In this issue of *Critical Care Medicine*, Dr. Mori and colleagues (10) set out to test the hypothesis that (in rats), in the face of ischemia caused by hemorrhagic shock, a free radical scavenger would reduce lipid peroxidation of neutrophils and this would preserve the integrity of the intestinal barrier, thereby preventing BT. Their chosen free radical sheriff was the 174.2-kD lipophilic edaravone. Edaravone has been shown to have protective effects against ischemia-reperfusion injury of most organs in animals (especially confirmed in rats) (11).

Using their well-practiced hemorrhagic shock rat model, this team have successfully demonstrated translocation of organisms and their products and an increase in SLP-activating substances (essentially peptidoglycans and β-glucans) following hypovolemic shock (10, 12). In this study, Dr. Mori and colleagues have convincingly demonstrated that edaravone reduced hemorrhagic shock-induced BT to the mesenteric lymph nodes and reduced hemorrhagic shock-induced peptidoglycan release (10). Is this relevant to our chosen animal, *homo sapiens*? Well, there is emerging evidence to support edaravone as a cardioprotective agent for myocardial reperfusion injury in humans (13). This cardioprotective and its neurovasculoprotective potential certainly address the case for clinical relevance.

Dr. Mori and colleagues (10) used the detection of 4-hydroxy-2-nenal-modified protein by immunohistochemistry on ileal sections as an index of free radical-induced lipid peroxidation, which purportedly reflected "oxidative stress." This is at best circumstantial evidence as free radicals were not measured directly. Links between "oxidative stress" and neutrophil damage, or support for a role for neutrophils in BT, are also speculative. BT and intestinal neutrophil lipid peroxidation could be epiphenomena.

Injury to the gut mucosa or vasculature will promote bacterial translocation. In hemorrhagic or hypovolemic shock, the mechanisms of gut injury are probably via severe gut hypoperfusion due to reduced circulating blood volume and cardiac output along with adrenergic splanchnic vasoconstriction, as well as ischemia-reperfusion injury. Unfortunately, Dr. Mori and colleagues did not attempt to measure splanchnic perfusion and therefore have not verified decreased gut perfusion in their study. However, other studies have correlated hemorrhagic shock with gut hypoperfusion (14), but splanchnic perfusion is a complex affair and not always directly related to intravascular volume (14, 15).

The spotlight on BT is principally based on the premise that BT is a pathologic mechanism for adverse outcomes in humans, a premise largely built on circumstantial evidence. BT may only be a marker of widespread injury in these hypoperfusion or hypovolemic scenarios. Ischemic and reperfusion effects are played out globally, yet oxidants generated during intestinal ischemia are presumed to enter the systemic circulation and predispose to distant inflammation (5, 9). Dr. Mori and colleagues (10) obtained bacterial cultures and showed an increase in SLP-reactive substance/peptidoglycan but failed to detect endotoxin. However, their previous study with the same hemorrhagic shock model and the same endotoxin technique obtained endotoxin levels (12). This raises questions concerning the franchise the gut holds as the origin and driving force behind widespread inflammatory effects. Unfortunately, Dr. Mori and colleagues did not assess lipid peroxidation in nonintestinal organs, for example, the lungs. I suspect there would be multiple-organ immune cell activation.

Dr. Mori and colleagues have not established a link between neutrophil oxidation and BT, but they have effectively demonstrated that edavarone, a "novel free radical scavenger," reduced BT and intestinal neutrophil lipid peroxidation following hemorrhagic shock in rats. Free radical scavengers have always held great clinical potential, stabilizing endothelial cells, addressing inflammatory cytotoxicity, reducing peroxidative damage, and dampening reperfusion injury. So, is this novel low molecular weight compound, edaravone, a vital component that we should include in our shock-pack in the field or merely an optional extra for the rat-pack? I will reserve judgment until the clinical trials in my preferred animal, *homo sapiens*, convert me.

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Improving the number and condition of donor lungs for transplantation*

For patients needing organ transplantation, whether pancreas, lung, liver, or kidney, there are simply not enough deceased or living related or unrelated organ donors. The shortage is exacerbated by the fact that not all donor organs are suitable for transplantation. This problem is especially severe for donor lungs, where the criteria presently used for acceptance exclude ≥80% as unsuitable for transplantation (1–3). This problem is, in turn, made worse by the fact that there is primary lung graft failure manifested as pulmonary edema, which is sufficiently severe in some 15% of lung transplant patients to cause acute respiratory distress syndrome with a mortality as high as 60%, and recovery, if it is possible, is often protracted (3).

In this issue of *Critical Care Medicine*, Dr. López-Aguilar and colleagues (4) explore one of the factors—massive brain injury—that they believe may predispose a given lung transplant to primary lung graft failure induced by ventilator-induced lung injury. Their findings have significance both for increasing the number of suitable donor lungs and for reducing the possibilities of primary lung graft failure.

Using a rabbit model, these investigators found that massive brain injury (induced by inflation of an intracranial balloon-tipped catheter to raise intracranial pressure above 150 mm Hg and cause brain herniation and electrocerebral silence within 20 mins) (5) resulted in lungs that, although initially similar to control lungs, demonstrated greater changes in ultrafiltration coefficient, weight gain, and alveolar hemorrhage, with each of these variables differing from those of the controls by $p < .05$. These changes were rapid, demonstrating the hidden difference between the control and brain-injury lungs within 30 mins of having been subjected to mechanical ventilation with peak airway pressure of 30 mm Hg and positive end-expiratory pressure of 5 cm H_2O.

At first glance, it is not surprising that massive brain injury, whether from external trauma or perhaps internal hemorrhage caused by infarction, hemorrhagic stroke, or a ruptured aneurysm, for example, can cause lung injury as manifested by alveolar edema (6–9). The important new finding of Dr. López-Aguilar and colleagues is that massive brain injury may predispose prospective donor lungs to further, significant injury from the ventilatory process used to maintain the lungs until they are removed for transplantation. This otherwise subtle, even grossly unapparent, altered lung state may result in the failure of donor lungs to meet the criteria for acceptability. Since alveolar edema interferes with oxygenation across the alveolar membrane, donor Po_2 may fall to or below 300 and thus render the lungs unacceptable (3). Transplanted lungs carrying this injury are undoubtedly more likely to be subject to primary graft failure and any further challenge (including immune) to their functional integrity. Also important to note from this discovery is the likelihood that something can be done to prevent or at least reduce this subtle injury.

The problem is that we need to know more, if we are going to be able to do something about this predisposition to further injury. Dr. López-Aguilar and colleagues did not evaluate candidate mechanisms. They do, however, suggest three possible mechanisms: increased circulating catecholamines; up-regulation of certain neuropeptides, such as substance P and neurokinin A (and neuropeptide Y) (10); and cytokine (such as tumor necrosis factor-α and interleukin-6) release. The lung parenchyma, as well as the bronchi and bronchioles, is well innervated by the afferent and efferent limbs of the autonomic nervous system (11, 12), and so direct measurement of sympathetic and parasympathetic nervous system activity, as well as receptors and neurotransmitter changes, could well provide valuable information. Still other mechanisms, such as depression of pulmonary antioxidants (13) and changes in nitric oxide levels (6), which may well be linked to altered autonomic activity secondary to brain stem compression from herniation, should also be considered. Certainly, further studies will need to include measurement of one or more of these and other possible variables in their design. In the meantime, careful attention to ventilatory protocols for the donors seems merited.

Finally, the optimal animal model for future studies needs careful thought. The rabbit model used by Dr. López-Aguilar and colleagues has, as they themselves discuss, limitations. The ventilation of the lungs after removal from the thoracic cavity means that the normal chest wall and diaphragm are gone, as are the lymphatic drainage system and the access of the donor immune system. The short period (120 mins) of *in vivo* ventilation of the lungs in the intact but brain-damaged

***See also p. 1077.**

Key Words: brain injury; donor lungs; brain death and injury; acute lung injury; mechanical ventilation; pulmonary edema; experimental animal models; lung transplantation.

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