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An Animal Model of Sepsis in Appendicitis: Assessment of the Microcirculation

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1. Introduction

Acute appendicitis is one of the most common causes of inflammation in the abdomen. Appendicitis, characterized by inflammation of the appendix, is an urgent clinical illness with significant morbidity, which increases with diagnostic delay. Perforation and peritonitis are associated with increased morbidity and mortality, especially in the very young, the elderly and immune-suppressed patients.

The diagnosis is based on the patient's history by the classic signs and symptoms of appendicitis (abdominal pain in the right iliac fossa, fever, anorexia, nausea, and vomiting) and physical examination. Children and the elderly have fewer signs and symptoms, or cannot adequate describe them. In pregnant women, particularly during the second and third trimester, the diagnosis of acute appendicitis is often delayed because of the nonspecific clinical abdominal presentation. In these conditions, diagnosis often requires imaging methods (ultrasound and/or CT scanning), and the incidence of complications is more frequent. Most patients usually recover well after surgical treatment, but complications can occur if treatment is delayed or if perforation that results in peritonitis or sepsis is present.

Sepsis and septic shock are clinical syndromes that result from complex interactions between the host and infectious agents. These events are characterized by hemodynamic derangements, widespread microcirculatory disturbances and cellular alterations leading to heterogeneous flow distribution, capillary obstruction and, therefore, to an uncoupling between cellular oxygen need and oxygen supply (De Backer et al., 2002; Hinshaw, 1996; Sakr et al., 2004). Despite improvements in treatments for sepsis, there are still gaps in our knowledge of the physiopathology and therapeutic interventions.

1.1 Cecal Ligation and Puncture as an experimental model of appendicitis

Among several experimental animal models, perforated appendicitis by cecal ligation and puncture (CLP), particularly in rodents, has been used to investigate the pathophysiology and assess the effectiveness of therapies in sepsis and septic shock. The CLP model begins with bowel exposure, followed by cecal ligation distal to the ileocecal valve. Thereafter, the cecum is perforated by a needle and the contents squeezed into the peritoneal cavity. The number of punctures, the diameter of the hole and the total amount of squeezed bowel content can introduce several variations of the model that will directly induce lethal or nonlethal sepsis. Sepsis in the CLP model is caused by contamination of the peritoneal cavity with a mixed flora of microorganisms and by the ischemic/necrotic tissue complications. Without the appropriate clinical (fluid resuscitation and antibiotics) and surgical treatment (necrotic tissue resection and peritoneal lavage), a rapid onset of septic shock can be observed.

1.1.1 Advantages of the CLP model

In this work, we will focus on the experimental model of CLP in rodents that is a simple and reproducible model widely used in research. The CLP model allows for control of the setting and reduction of some of the variables. We have focused on the mechanisms responsible for the altered immunological, cardiovascular, respiratory and metabolic changes as a model for acute perforated appendicitis in humans.

The CLP model can also be used to evaluate cardiac output/total and regional blood flow (Angle et al., 1998; Jarrar et al., 2000; Yang et al., 2002), metabolism (Lang et al., 1990; Wang et al., 1999), immune function (Ayala & Chaudry, 1996; Kato et al., 2004; Schneider et al., 2000), apoptosis (Reddy et al., 2001; Ayala &Chaudry, 1996; Chung et al., 2003; Coopersmith et al, 2002), cytokines (Schneider et al., 2000; Vianna et al., 2004), resuscitation (Esmon, 2004; Marx et al., 2004; Yang et al., 2002), antibiotics (Doerschug et al., 2004; Vianna et al., 2004), and microbial components (Ayala & Chaudry, 1996; Esmon, 2004; Mollitt, 2002; Yang et al., 2001).

1.1.2 Limitations of the CLP model

The CLP model in small mammals, particularly rodents, has some limitations on the translation to humans. One difference that is common between rodents and humans is that the mice or rats can tolerate quite well the cecal ligation alone without puncture. These animals can block the necrotic tissue and survive. Humans, in turn, are not able to overcome by theirselves. Another aspect is related to the size of the animal. Several technical and physiological difficulties may appear. Among them, the inability to obtain large quantities of blood and other fluids for tests over long periods of observation (Hubbard et al., 2005), and the technology to obtain accurate physiological measurements in these small animals.

1.2 Other models of acute appendicitis

Rabbits and pigs have also been used as experimental models of acute appendicitis. However, due to anatomical differences, the use of pigs is very limited. Pig does not have an appendix and the occlusion is performed in the uterine horn to study surgical procedures, such as an endoscopic transgastric appendectomy (Sumiyama et al., 2006) . In rabbits, investigators use the vascular partial or total clamping method to obtain necrotic tissue mimicking the acute appendicitis (Nunes & Silva, 2005).

2. Intravital microscopy in the assessment of microcirculation

A well-established technique applied in many experimental models of sepsis is the intravital microscopy (Figure 1). This technique allows the *in vivo* and *in situ* observation of the microvascular bed of different tissues, such as the mesentery, ileum, liver, and skeletal muscle of rats, mice, rabbits and felines. Suitable tissues are selected if they can be easily exteriorized and transilluminated, as illustrated in Figure 2. It is important to minimize the preparative surgery and to maintain the physiological conditions: temperature, extracellular fluid composition, pH, and gas tensions. The introduction of close circuit television has facilitated quantification of many of the variables, such as leukocyte-endothelial interactions, through the possibility to store images on videotape for detailed off-line analysis. More recently, analyses have been performed online by using image-computer software (Nakagawa et al, 2006).

Fig. 1. Equipment for Intravital Microscopy.

Intravital microscopy has been applied to evaluate different pathophysiological aspects of the microcirculation during several challenges. In addition, intravital microscopy has also been used to test novel prophylactic and therapeutic approaches that aim to prevent or attenuate manifestations of sepsis-associated microvascular disorders and cellular dysfunctions. In the mesentery, microcirculatory observations have focused on capillary obstruction, capillary or arteriolar density, microvessel reactivity and leukocyte-endothelial interactions in post-capillary venules (Harris, 2006; Kim & Harris, 2006; Nakagawa et al., 2006, 2007; Schimidt et al., 1997; Smalley et al., 2000; Walther et al., 2004; Woodman et al., 2000). A representative photomicrograph of rat mesenteric microcirculation is shown in Figure 3. In other organs, such as lungs and heart, increased leukocyte-endothelial interactions have been observed mostly induced by physical trapping in pre-capillary microvessels and capillaries (Kubo et al., 1999; Waisman et al., 2006). In liver, blood flow/perfusion regulation is at the arteriolar and sinusoidal level (Baveja et al., 2002; Kamoun et al., 2005).

Microcirculatory dysfunctions, as seen in humans (De Backer & Dubois, 2001; De Backer et al., 2002; Groner et al., 1999; Trzeciak et al., 2007), have been shown to occur in most experimental models of sepsis (Baveja et al., 2002; Kamoun et al., 2005; Kim & Harris, 2006; Kubo et al., 1999; Nakagawa et al., 2006, 2007; Nakajima et al., 2001; Schimidt et al., 1997; Smalley et al., 2000; Waisman et al., 2006; Walther et al., 2004; Woodman et al., 2000). Endotoxin infusion is a widely used experimental model (Kim & Harris, 2006; Schimidt et al., 1997; Smalley et al., 2000; Nakajima et al., 2001). Increased leukocyte-endothelial interactions and protein leakage in mesenteric microvessels have been shown to occur after acute endotoxemia in rats (Schimidt et al., 1997; Woodman et al., 2000) and cats (Walther et al., 2004). However, there are two major concerns regarding this experimental model: 1) clinical sepsis typically evolves over many days, in contrast to studies on the early effects (1 to 6 hours) of endotoxin administration, and 2) rats are generally more resistant to the effects of endotoxin.

Fig. 2. Positioning of the mesentery in the platform for intravital microscopy.

Therefore, many microvascular changes seen in animal models of endotoxemia may not occur in humans (Chaudry, 1999). On the other hand, laparotomy complicated by sepsis is a common clinical presentation of sepsis. This rationale was used in selecting CLP as a model of polymicrobial and normotensive sepsis (Chaudry, 1999; Chaudry et al., 1979; Farquhar et al., 1996; Hersch et al., 1998; Madorin et al., 1999; Nakagawa et al., 2006, 2007).

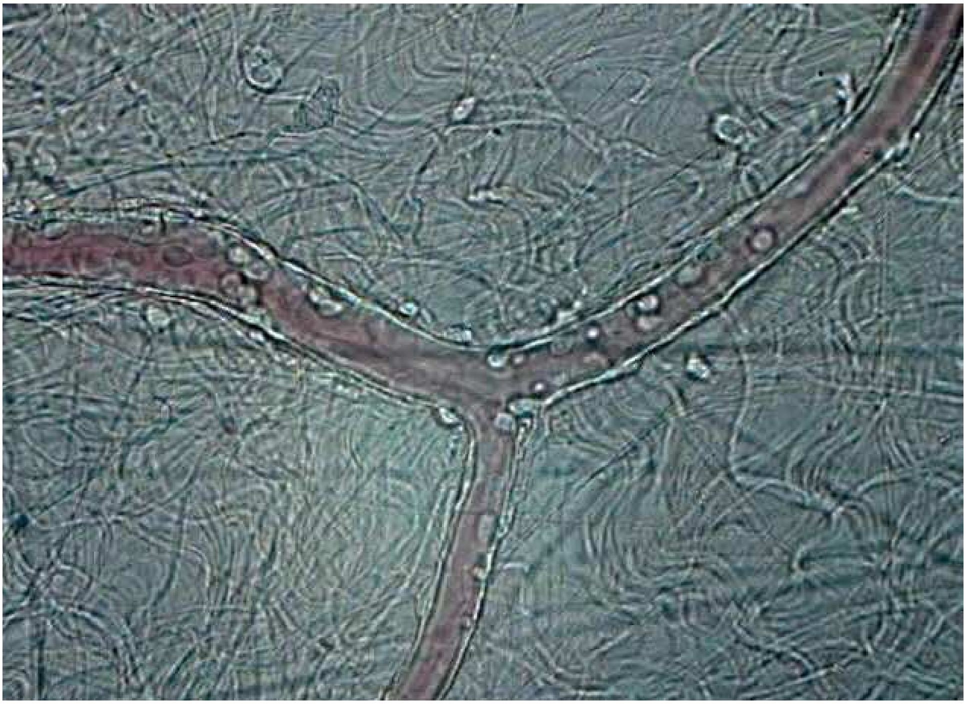

Fig. 3. Photomicrograph of rat mesenteric microcirculation by intravital microscopy showing leukocyte-endothelial interactions under inflammation (425x)

In the CLP model (Figure 4), many microvascular derangements occur such as increased total blood flow to the ileum with preferential redistribution toward the muscularis and away from the mucosa (Farquhar et al., 1996; Hersch et al., 1998; Madorin et al., 1999; Nakajima et al., 2001). The abnormal microvascular blood flow may result in tissue hypoxia and increased permeability (Farquhar et al., 1996). CLP induces an inflammatory response characterized by an increased number of white blood cells, increased leukocyte-endothelial interactions in mesenteric microvessels and lung neutrophil infiltration (Nakagawa et al., 2006).

3. CLP in a double-injury model

In attempting to understand the pathophysiology of septic shock, several investigators have performed double-injury models to study the microcirculation by intravital microscopy in different tissues. Hoffman et al. (1999) observed increased leukocyte adhesion and reduced capillary perfusion in skin microvessels of hamsters submitted to persistent endotoxemia (72 hours) induced by a double-LPS exposure**.** Swartz et al. (2000) performed CLP followed by the local application of *E. coli* on cremaster muscle. Despite an intra-abdominal infection, there was no increase in leukocyte adhesion in the cremaster muscle. In contrast, Pascual et al. (2003) observed increased leukocyte adhesion to microvessels of cremaster muscle after hemorrhagic shock/reperfusion followed by intratracheal injection of LPS in mice. Smalley et al. (2000) reported no changes in leukocyte adhesion in the mesentery in an acute model (4 hours) of CLP. However, a topical application of highly diluted fecal matter increased leukocyte adhesion in the mesenteric microcirculation, which was mediated by platelet activation factor. More recently, Nakagawa et al. (2006) observed leukocyte-endothelium interactions in the mesenteric microcirculation after hemorrhagic shock/reperfusion followed by an intra-abdominal sepsis (CLP). Twenty-four hours after the double-injury, rats exhibited an increased number of rolling, adherent and migrated leukocytes accompanied by an increased expression of P-selectin and intercellular adhesion molecule (ICAM)-1 at the mesentery and by leukocyte infiltration and ICAM-1 up-regulation at the lungs.

Fig. 4. Twenty-four hours after cecal ligation and puncture model. Note the impressive intestinal edema around the necrotic tissue.

4. Surgical control of the septic focus

In the model of single-injury (CLP) the surgical removal of the septic focus followed by peritoneal lavage partially controls the inflammatory reaction in these animals. By intravital microscopy, leukocyte-endothelial interactions at the mesentery were normalized by the surgical control. These results support surgical source control as a therapy contributing to resolving the immune dysfunction observed in this specific septic challenge (Nakagawa et al., 2007).

5. Conclusion

Cecal ligation and puncture in rodents is a useful experimental model that mimics appendicitis with pathophysiological alterations enrolled in this process. Surgical removal of the septic focus improves clinical condition and normalizes physiological aspects that are clearly observed in this model. In addition, the study of the microcirculation by intravital microscopy represents a unique research tool to analyse complex biological interactions and disease-related mechanisms.

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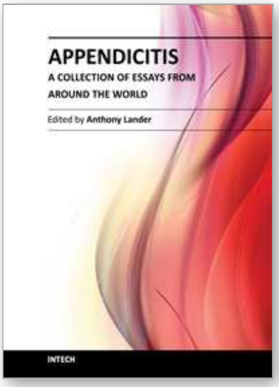

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This book is a collection of essays and papers from around the world, written by surgeons who look after patients of all ages with abdominal pain, many of whom have appendicitis. All general surgeons maintain a fascination with this important condition because it is so common and yet so easy to miss. All surgeons have a view on the literature and any gathering of surgeons embraces a spectrum of opinion on management options. Many aspects of the disease and its presentation and management remain controversial. This book does not answer those controversies, but should prove food for thought. The reflections of these surgeons are presented in many cases with novel data. The chapters encourage us to consider new epidemiological views and explore clinical scoring systems and the literature on imaging. Appendicitis is discussed in patients of all ages and in all manner of presentations.

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