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Gut mucosal permeability, β_1 receptor blockers and gastric tonometry: the time is now!

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In addition to its primary role as an organ of nutrient absorption, the intestinal mucosa prevents toxic luminal contents from entering the blood stream. Increases in mucosal permeability result from damage to the enterocyte or to their tight junction. Loss of mucosal integrity leads to bacterial and cytokine translocation with the development of the systemic inflammatory response syndrome, sepsis and multiple organ failure [1].

Therapy designed to prevent or ameliorate mucosal disruption has encountered little success. In the article by Mori et al. [2] in this issue of *Intensive Care Medicine*, the selective β_1 receptor blocker esmolol was administered to rats that had undergone cecal ligation and perforation. Compared to a sham control, esmolol-treated rats had significantly longer survival, lower mucosal injury scores, fewer positive mesenteric lymph nodes for *E. coli* and lower levels of TNF α in the intraperitoneal fluid. Although preliminary and experimental, the finding is important given the familiarity most clinicians have with selective β_1 receptor blockers.

A practical difficulty associated with therapy designed to prevent intestinal mucosal damage is how best to assess its effectiveness. Noninvasive markers of intestinal mucosal barrier integrity recently have become available.

Plasma levels of intestinal-fatty acid binding protein (I-FABP), a cytosolic protein found mainly in mature enterocytes, correlates with damage to these cells during intestinal ischemia and inflammation [3, 4]. Ileal-bile acid binding protein (I-BABP), found exclusively in jejunal and ileal enterocytes [5, 6], is another blood marker of enterocyte integrity. Urinary levels of claudin-3, a trans-membrane sealing protein, provide a measure of tight junction integrity [7]. Finally, fecal calprotectin, a calcium- and zinc-binding protein found in ileal tissue monocytes, macrophages and eosinophils, appears to be a sensitive marker of activity in inflammatory bowel disease [8, 9].

We doubt these tests will be useful as monitors of evolving mucosal dysfunction in critically ill individuals. Fecal and urinary samples are difficult to obtain following severe episodes of hypotension or sepsis. Moreover, laboratory analysis may take too long for their results to be actionable. The ideal monitor of mucosal dysfunction should be noninvasive, timely, easily understood, and associated with a therapeutic response. We find it curious that gastric tonometry, a monitoring tool meeting many of these requirements and available to clinicians for the past quarter century, is no longer used.

The gastric tonometer is a nasogastric tube with a balloon at the end that, once inserted in the patient's stomach, is filled with saline or air. After a suitable equilibration period, the balloon PCO₂ approximates that of the mucosa. Increases in mucosal PCO₂ correlate with disruption of mucosal blood flow [10] and are strongly associated with poor outcome [11]. The development of gastric tonometry is traced to Boda and Murányi [12] who used it as a surrogate for arterial PCO₂ in mechanically ventilated children. Gastric tonometry was forgotten until rediscovered by Richard Fiddian-Green when studying intestinal mucosal ischemia [13]. A great deal of research followed, generating much interest in the clinical community. Today, typing “gastric tonometry” in Google

Scholar returns 5,090 articles, including a prospective interventional ICU trial in which therapy guided by gastric tonometry showed survival benefits [14]. Why was gastric tonometry abandoned? The answer is too long and complex to be fully addressed in this editorial. Although technical problems plagued tonometry from its inception,

the main reason appears to have been lack of a clearly defined therapeutic response. Perhaps we have reached the stage where a clinical trial of β_1 receptor blockers should be undertaken along with a revival of gastric tonometry.

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