Morphological Features Of The Gastric Mucosa In Critically Ill Patients On Artificial Lung Ventilation

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ABSTRACT

It has long been known in medical practice that the gastrointestinal tract (GIT) fulfils not only digestive function. The GIT tract is also an important endocrine organ that synthesises many hormones involved in the regulation of protein, fat and carbohydrate metabolism, having a systemic effect on the body. The walls of the gastrointestinal tract contain about 100 million neurons that constantly control its activity, as well as about 60-70% of the body's lymphoid tissue, which plays a key role in immune defence. There are convincing data supporting the link between the GI tract condition and the development of systemic inflammatory response, as well as multi-organ failure, which is due to disturbances of microcirculation in the villous layer of the intestine and high sensitivity of tissues to hypoxia (Swank G.M., Deitch E.A., 1996). This study emphasises the relevance of studying the gastric mucosa in critically ill patients on artificial ventilation.

It should also be noted that in recent years the mechanisms of influence of the intestinal microbiota on the general state of the organism have been actively studied. Disruption of the barrier function of the gastrointestinal mucosa can contribute to the penetration of bacteria and toxins into the systemic bloodstream, which enhances inflammatory processes and increases the risk of sepsis. Thus, maintenance of mucosal integrity and adequate microcirculation plays a crucial role in the prevention of complications in critically ill patients.

Keywords: hypoxia, lymphoid tissue, inflammatory process, erosions, ulcers, microbiota, barrier function.

Introduction

The stomach has traditionally been viewed as a hollow, muscular organ involved in the second stage of digestion. However, this oversimplified perspective overlooks its role as a complex endocrine organ with distinctive physiological, biochemical, immunological, and microbiological features. The stomach's secretion of gastric juice serves not only to initiate digestion but also acts as a crucial defense mechanism against ingested pathogens [1].

In the early 20th century, extensive studies of gastric secretion regulation were carried out through cranial vagotomy and resection of the celiac trunk, which were used as therapeutic interventions. These experiments revealed the intricate regulatory mechanisms of gastric function and sparked significant interest in Dale and Laidlaw's research on histamine [2]. This line of investigation led to Popielski's discovery of histamine's role in stimulating gastric secretion [3], followed by the discovery of secretin by Bayliss and Starling [4], and Adkins' detailed work on gastrin [5].

The digestive system is highly sensitive to adverse factors. The stomach wall comprises four layers: the serous membrane, muscular membrane, submucosal layer, and mucosa. Some authors describe the stomach as having three layers (mucosa, muscularis, and serosa), while others consider the well-developed submucosa as a distinct fourth layer. The gastric mucosa is characterized by structures such as gastric pits, folds, and microvilli [6]. The gastric fields range from 1 to 5 mm in diameter, and the stomach contains approximately 4 million gastric pits. Although the stomach's muscular layers are present from birth, the longitudinal and oblique fibers remain underdeveloped until around 15-20 years of age, when the muscular coat reaches its full thickness. The stomach contains five types of cells and has a well-developed glandular system responsible for the secretion of hydrochloric acid, mucus, bicarbonates, and intrinsic factor [7].

The gastric mucosa possesses unique properties: its glands secrete 2-3 liters of gastric juice per day. This secretion is primarily composed of pepsinogen produced by chief cells and hydrochloric acid (HCl) secreted by the parietal cells in the body and fundus of the stomach. The cardiac and pyloric regions of the stomach secrete mucus (mucin). Gastric juice, which is stimulated by food intake, is isotonic to blood, has a highly acidic pH (0.8-1.5), and contains not only intrinsic factor but also gastrin, acetylcholine, histamine, prostaglandins, lipase, as well as sodium, potassium, magnesium cations, and $HPO4^{2}$- and $SO4^{2}$- anions [8].

Numerous clinical and morphological studies have highlighted that the gastrointestinal tract is one of the first organs to be affected during shock [9]. Long-term investigations into intestinal permeability and its role in disease development have identified the following key points: 1) disruption of the intestinal barrier is linked to various diseases, 2) malnutrition increases intestinal permeability, and 3) adequate nutrition plays a pivotal role in maintaining intestinal barrier integrity [10]. Despite its critical importance, the gastrointestinal tract often remains an overlooked organ in emergency care settings [11].

In patients receiving artificial ventilation, delayed gastric emptying has been observed in up to 87% of cases. However, accurately measuring the rate of gastric emptying in these patients poses significant technical challenges.

Several risk factors contribute to delayed gastric emptying, including the severity of illness, patient age, increased intracranial pressure, reduced Glasgow Coma Scale score, time since brain injury, and the extent of spinal cord injury [12]. Opioids appear to have a more significant impact on delaying gastric emptying compared to non-opioid sedatives, as confirmed by scintigraphic findings. Patients receiving propofol had a significantly shorter gastric half-emptying time and reduced food retention compared to those receiving a combination of midazolam and fentanyl [13].

In recent years, there has been a growing body of literature examining the brain's specific influence on gastrointestinal (GI) function, the condition of the mucosal lining, and the intestinal microbiota. A study by V. Singh et al. modeled ischemic stroke in the middle cerebral artery and found that severe brain injury leads to reduced GI motility, associated with bacterial overgrowth and a decline in microbiota diversity. Despite this functional disruption, there was no evidence of bacterial translocation or invasion into the intestinal mucosa, suggesting that the intestinal barrier remained morphologically intact. Conversely, less extensive cortical damage did not result in microbiome alterations or intestinal paresis [14].

Neurological deterioration and reduced vital signs are often associated with increased gastric acid secretion, driven by heightened parasympathetic activity. This hyperacidity can result in the development of erosions and gastrointestinal bleeding. Hemorrhages may arise from fresh esophageal, gastric, or duodenal ulcers, or from multiple erosions in the gastric mucosa. In some cases, patients present with dilated vessels, epithelial desquamation, and hemorrhages affecting the mucosa or the entire gastric wall. The incidence of gastrointestinal bleeding in patients with

prolonged unconsciousness ranges from 5% to 11% [15].

Erosive and ulcerative lesions of the stomach and duodenum are observed in 75% (ranging from 40% to 100%) of patients during the early hours of their stay in the intensive care unit (Raynard B., Nitenberg G., 1999; Fennerty M.V., 2002). The etiological factors contributing to these lesions, from the disruption of mucosal integrity (stress gastritis → stress ulcers) to motility disorders and swelling (hypoalbuminemia), are collectively referred to as acute gastric injury syndrome (AGI) (Gelfand B.R. et al., 2004). The development of multi-organ dysfunction in conjunction with severe traumatic brain injury significantly worsens the overall prognosis (Leiderman I.N., 1999).

In cases of severe cranio-cerebral trauma (CCT), the gastrointestinal tract encounters multiple dysfunctions. The first issue is hypovolemia. As a result of circulatory centralization, the GI tract is the first system to experience ischemia and the last to regain adequate perfusion during treatment for volume-related disorders. Ischemia of the gastric and intestinal mucosa can lead to erosions and acute ulcers, potentially causing gastrointestinal bleeding, which exacerbates hypovolemia and contributes to the vicious cycle often seen in intensive care settings. The second issue involves neurological impairments. Damage to the diencephalon and the caudal group of cranial nerves disrupts the innervation of the pharynx, esophagus, stomach, and intestines, leading to paresis of these organs. Brainstem dysfunction caused by displacement or secondary pathological effects (hypoxia, hypocapnia, hyperthermia, or purulent-septic complications) further exacerbates digestive disorders and leads to gastric stasis. Prolonged stasis increases the risk of stress erosions in the stomach and duodenum, often accompanied by bleeding.

A third factor contributing to gastrointestinal (GI) dysfunction is hypokalemia, which arises from various causes, including volaemic and neurohumoral disturbances, inappropriate use of diuretics, insulin administration for hyperglycemia control, and excessive diuresis induced by sympathomimetics. The duration and severity of gastric and intestinal paresis can vary widely. While intestinal motility often recovers, gastric content stasis may persist. Additionally, motility disorders can manifest as antiperistalsis due to uncoordinated muscle sphincter function [16].

These conditions create an environment for gastric content regurgitation into the esophagus and oral cavity. The presence of bulbar and pseudobulbar disorders further increases the risk of aspiration of these contents into the respiratory tract, a major pathway for the development of pulmonary inflammatory conditions. Additionally, the dysfunction in gastric and intestinal motility results in gastric and intestinal dilation, causing upward displacement of the diaphragm. This displacement leads to respiratory complications, including reduced lung capacity, impaired lung compliance, and an increased risk of atelectasis. The resulting hypoxia exacerbates the GI condition [17].

GIT motility impairment poses significant risks, as it restricts the patient's ability to consume food. The absence of food in the GIT lumen results in several detrimental effects: firstly, the ongoing secretion of hydrochloric acid and digestive enzymes irritates the mucosa, further contributing to ulcer and erosion formation; secondly, the lack of nutrient intake deprives the body of energy substrates, which are critically needed in a state of increased metabolic demand; thirdly, the lack of nutrition disrupts the supply of essential nutrients to the intestinal wall, depriving enterocytes of necessary nourishment. Combined with intestinal ischemia caused by hypovolemia, this situation increases intestinal permeability, allowing microorganisms to translocate from the gut lumen into the portal and systemic circulation. This process, known as bacterial translocation, is considered a potential mechanism for the development of septic complications (Connolly A.B., Vernon D.R., 2000).

Septic bowel paresis is thought to be caused by cytokine-mediated inhibition of intestinal smooth muscle cells and suppression of enteric neuromuscular transmission [18]. External risk

factors contributing to this condition include medications commonly used in intensive care (e.g., sedatives, opioid analgesics, vasopressors), electrolyte imbalances, and stress-induced hyperglycemia [19, 20]. Additionally, the composition and method of enteral nutrition administration, whether bolus or continuous drip, have a significant impact on gastric emptying and nutrient movement [21-23].

Research into damage processes in the gastroduodenal region remains an area of active morphological, clinical, and endoscopic investigation (Aruin L.I., 1998; Golofeevsky V.Y., 2005; Vasiliev Y.V., 2008). Key contributors to the development of mucosal defects include stress-related factors (Maslova M.N., 2005; Kalinin A.B., 2004, 2008) and the adverse effects of medications, particularly non-steroidal anti-inflammatory drugs and glucocorticoids (Gurin H.H., 1998; Polunina T.E., 1997; Vasiliev Y.V., 2003; Bandurina T.Y., 2004; Tkachenko E.I., 2006).

Delayed gastric emptying is a frequent occurrence, likely driven by the effects of cholecystokinin and reduced active ghrelin levels. The mechanisms underlying impaired nutrient absorption remain poorly understood but may involve altered blood flow in the small intestine or compromised mucosal barrier function. The impact of critical illness and its associated treatments on macronutrient absorption varies depending on the nutrient in question [24]. While the optimal amounts of energy and protein for critically ill patients remain a subject of debate, enteral nutrition is widely recognized as a cornerstone of nutritional support in this population.

GIT motility impairment in critically ill patients has several significant clinical consequences, with impaired nutrient delivery being the most prominent. Certain patient populations, such as those with combined trauma (60%), brain injury (57%), or sepsis (42%), are at an increased risk of developing nutritional intolerance and delayed gastric emptying [25].

The clinical presentation of gastrointestinal dysfunction associated with critical illness includes reduced glucose absorption from the small intestine in patients with significant gastric residual volumes. Intestinal dysfunction is characterized by a combination of delayed gastric emptying, impaired nutrient absorption in the small intestine, and disrupted peristalsis of both the small and large intestines, which can manifest as either constipation or diarrhea [26]. Despite its variability, small bowel transit generally remains normal in critically ill patients [27, 28], allowing differentiation from intestinal obstruction (non-mechanical obstruction of the small or large intestines), which is less commonly observed in this patient population [29].

Recent studies on critically ill patients undergoing prolonged mechanical ventilation (MV) and receiving nonsteroidal anti-inflammatory drugs (NSAIDs) have shown that the effects of NSAIDs on the stomach lead to selective damage between the parenchyma and stroma [30]. These changes are likely due to a specific response of the stomach to the local administration of NSAIDs, resulting in weakened immune defenses, provocation of allergic reactions, promotion of antibiotic resistance, reduced treatment efficacy, and the development of pathologies related to the accumulation of substances in the body [31].

In critical care patients in intensive care units (ICUs), the mucus-bicarbonate barrier of the stomach can break down within minutes, leading to epithelial cell death, the development of edema, and hemorrhages into the gastric mucosa [32]. Disruption of the stomach's protective mechanisms in these conditions results in what is referred to as acute gastric injury syndrome (AGI), analogous to acute lung injury syndrome (ALI). AGI is characterized by edema, mucosal barrier disruption, and impaired gastric motility, occurring in 75% (ranging from 40% to 100%) of critically ill patients [33-35].

The primary causes of gastric mucosal injury include localized ischemia and reperfusion, accompanied by excessive production of nitric oxide, reactive oxygen species, cytokines, and a reduction in protective prostaglandin synthesis. These processes lead to the death of epithelial cells and suppression of their regeneration [36]. Gastric paresis develops in

50-80% of patients, despite the preservation of normal intestinal peristalsis.

Gastroparesis arises from multiple factors, including disruptions in the synthesis of pain and inflammation mediators (e.g., cytokines and kininogens), enteroneuronal disturbances (sympathicotonia, the action of gastric inhibitory peptide and cholecystokinin), ischemia and reperfusion, the impact of bacterial endotoxins, and the effects of medications (e.g., narcotics, low doses of dopamine). The multifactorial nature of gastroparesis accounts for the limited efficacy of pharmacotherapy. Mucosal edema, often associated with hypoproteinemia, leads to impaired absorption of nutrients and medications in the gastrointestinal tract, further compromising the protective properties of the mucosal barrier and reducing its resistance to the harmful effects of gastric acid.

Gastrointestinal (GI) injuries in critically ill patients on mechanical ventilation (MV) in the intensive care unit (ICU) can be classified into two main types:

I. Superficial diffuse erosions, which carry a low risk of bleeding.

II. Deep localized ulcers with a high risk of hemorrhagic complications, with an incidence of 14% in ICU patients and a mortality rate of 64% in these cases [37].

GI bleeding most commonly occurs within the first 8 days of ICU admission, with an average onset around day 4. Based on the severity of bleeding, the following categories can be distinguished:

I. Occult bleeding, where blood is detected in gastric contents or stool, but there are no clinical manifestations.

II. Overt bleeding, characterized by the presence of whole blood or "coffee grounds" in gastric aspirate, as well as blood in the stool or melena.

III. Clinically significant bleeding, marked by overt bleeding accompanied by hemodynamic instability lasting more than 24 hours, often requiring blood transfusion and, in many cases, surgical intervention.

It is important to note that during bleeding episodes, gastric acid and pepsin may inhibit thrombus formation and promote lysis of already formed clots. Platelet aggregation, which is critical for platelet-vessel hemostasis, occurs at a pH level above 6.0 [38].

CONCLUSION

In summary, the morphological characteristics of the gastric mucosa in critically ill patients on prolonged mechanical ventilation are marked by significant alterations associated with their critical condition and the intensive therapies they undergo. Destructive changes such as edema, hyperemia, erosions, and ulcers of the gastric mucosa are observed, resulting from both physical and chemical factors during extended MV. Impairments in gastric secretion regulation, the effects of medications, and hypovolemia further exacerbate mucosal damage, potentially leading to the development of acute gastric injury syndrome (AGI). Understanding these processes and their consequences is crucial for effectively managing the patient's condition and preventing serious complications. Continuous monitoring and appropriate therapeutic interventions are essential to mitigate further damage and improve outcomes in critically ill patients.

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