Perioperative Intestinal Injury: Etiology, Mechanism, and Prevention

3

Xiao-Dong Chen and Ke-Xuan Liu

Abstract

Perioperative organ injury is a severe and commonly encountered problem in surgical practice and has been drawing great attention from physicians and researchers. Under the philosophy of precision medicine and fast-track surgery, anesthesiologists have direct influence on patients' long-term outcomes by protecting important organs during perioperative period. This will reflect the evolvement of anesthesiology to perioperative medicine. There had been widespread concern over the mechanism and prevention of perioperative heart, brain, lung, and kidney injuries. Whereas the intestine is a luminal organ, research interests were often put to its digestive, absorbing, and excretory functions. In fact, intestines have much more functions than that mentioned above; intestine barrier has complex components, which can be easily affected by internal or external factors such as ischemia, hypoxia, infection, stress, or prolonged administration of antibiotics or immunosuppressants. Among these factors, intestinal ischemia is the most common cause of perioperative intestinal injury; this process not only occurs during the hypoperfusion stage but more importantly after blood supply was restored, namely, ischemia/reperfusion injury. The further intestinal injury caused by reperfusion and the consequent extraintestinal organ injuries were called second hit. The impaired intestinal mucosal barrier and subsequent translocation of intestinal bacteria and endotoxin can result in systemic inflammatory reaction syndrome. Here, we review the progress in the study of the mechanism, prevention, and treatment of perioperative intestinal injury (especially intestinal I/R injury), hoping to provide some useful information for clinical practice.

X.-D. Chen · K.-X. Liu (✉)
Department of Anesthesiology, Nanfang Hospital, Southern Medical University, Guangzhou, P. R. China

X. Fu, L. Liu (eds.), *Severe Trauma and Sepsis*,
https://doi.org/10.1007/978-981-13-3353-8_3

Perioperative organ injury is a severe and commonly encountered problem in surgical practice and has been drawing great attention from physicians and researchers. Under the philosophy of precision medicine and fast-track surgery, anesthesiologists have direct influence on patients' long-term outcomes by protecting important organs during perioperative period. This will reflect the evolvement of anesthesiology to perioperative medicine.

There had been widespread concern over the mechanism and prevention of perioperative heart, brain, lung, and kidney injuries. Whereas the intestine is a luminal organ, research interests were often put to its digestive, absorbing, and excretory functions. In fact, the intestines have much more functions than that mentioned above; intestine barrier has complex components, which can be easily affected by internal or external factors such as ischemia, hypoxia, infections, stress, or prolonged administration of antibiotics or immunosuppressants. Among these factors, intestinal ischemia is the most common cause of perioperative intestinal injury; this process not only occurs during the hypoperfusion stage but more importantly after blood supply was restored, namely, ischemia/reperfusion injury. The further intestinal injury caused by reperfusion and the consequent extraintestinal organ injuries were called second hit. The impaired intestinal mucosal barrier and subsequent translocation of intestinal bacteria and endotoxin can result in systemic inflammatory reaction syndrome. Some hypovolemic shock patients died of severe lung complications even after blood pressure and urine volume had been recovered by anti-shock treatment. The reason was related to lung injury after intestinal I/R. Therefore, intestinal mucosal barrier damage usually occurs earlier than other organs; the intestinal tract is named "the triggering organ" and "the central organ of the surgical stress response." However, the importance of intestinal injury was often overlooked in clinical practice. Moreover, the mechanism of intestinal I/R injury remains unclear, and effective prevention and treatment is lacking. Here, we review the progress in the study of the mechanism, prevention, and treatment of perioperative intestinal injury (especially intestinal I/R injury) and extraintestinal organ damage, hoping to provide some useful information for clinical practice.

3.1 Etiology of Perioperative Intestinal Injury

3.1.1 Trauma and Shock

Traumatic-hemorrhagic shock is the main cause of death for people under the age of 45. It has been proved that if hemorrhagic shock could not be corrected in time, 51–61% of patients would eventually die of multiple organ failure (MOF) later, even though they survived the most dangerous phase of the pathophysiological changes. During hemorrhagic shock resuscitation, intestinal barrier function would be damaged because of the disproportionately decreased blood flow to the gut. The severe intestinal ischemia/reperfusion injury would be followed by bacterial translocation and endotoxemia, which led to systemic inflammation

via the intestine-liver-lung or intestine-lymph-lung path. The systemic inflammation would eventually lead to multiple organ failure (MOF) [1]. Even though the mesenteric artery can maintain blood flow relatively stable within a certain range of blood pressure, when blood pressure becomes under 40–45 mmHg, intestinal perfusion is compromised. Intestinal epithelial cellular injury in humans is detectable by 20 min of total mesenteric ischemia or within 60 min in the case of partial mesenteric ischemia [2]. Some vasoactive agents such as vasopressin, digoxin, phenylephrine, dopamine (high dose), and epinephrine (high dose) applied during shock resuscitation may also significantly reduce the intestinal blood supply [3].

3.1.2 Acute Pancreatitis

The intestinal injury caused by acute pancreatitis is mainly related to lowered mesenteric blood flow and decreased pHi of the intestinal mucosa. The small intestine may be damaged during severe acute pancreatitis, due to hypovolemia, splanchnic vasoconstriction, microcirculation disturbance associated with fluid loss in the third space, and finally ischemia/reperfusion injury [4]. SAP (severe acute pancreatitis) patients with abdominal compartment syndrome (intra-abdominal pressure IAP >20 mmHg) had an increased risk for intestinal ischemia. In SAP patients, release of inflammatory cytokines such as diamine oxidase and TNF-α leads to ischemia/reperfusion injury of gut mucosa which results in serious oxidative stress and activation of caspase-3 pathway and enhances epithelial cell apoptosis [5]. Elevated serum HMGB-1 (high-mobility group box 1) levels in SAP patients contribute to intestinal hyperpermeability and facilitate bacterial translocation and systemic inflammation [6].

3.1.3 Cardiac Surgery and Cardiopulmonary Bypass

De Silva et al. reviewed 348 patients by postmortem examination of 363 deaths from a total of 10,099 cardiac surgery performed over a 7-year period and found that among 52 patients whose actual primary cause of death was gastrointestinal (GI) origin, 45 patients died of intestinal ischemic injuries [7]. CPB leads to intestinal injury and is associated with hypoperfusion of the intestine. The exposure of blood to artificial materials used in the circuit and the altered blood flow and temperature may also activate inflammatory response. This can lead to ischemic damage in sensitive organs like the intestine [8]. It is reported that the endotoxin concentration in plasma can peak at 30 min after bypass and lasts for 20 h. Adamik et al. reported the serum endotoxin concentration elevated in 73% of patients with CPB time >90 min and 33% with CPB time <90 min, and their findings implied that intestinal ischemia/reperfusion injury occurred in all patients during cardiopulmonary bypass, but the magnitude of the intestinal damage depended on the duration of the cardiac bypass time [8].

3.1.4 Abdominal Aortic Aneurysm (AAA) Repair

Both open and endovascular (EVAR) AAA repair can cause bowel ischemia; the incidence rate is 1–3% for open and 0.5–3% for endovascular AAA repair, respectively. Ultee et al. reported that ruptured AAA was the most important determinant of postoperative bowel ischemia followed by open repair. Additional risk factors including patient characteristics were venerable age, female gender, hypertension, heart failure, and current smoking. Other risk factors from procedure features included unilateral interruption of the hypogastric artery, prolonged operative time, blood loss >1 L, and a distal anastomosis to the femoral artery. Bowel ischemia patients had a significantly higher perioperative mortality after intact as well as after ruptured AAA repair [9].

3.1.5 Liver Surgery

Intestinal injury may occur in liver operations, which is mainly related to hepatic portal occlusion. It was also reported that plasma endotoxin concentration was significantly related to hepatic portal occlusion. Li et al. retrospectively analyzed 1329 patients undergoing hepatectomy and found that the incidence of gastrointestinal complications reached 46.4% [10] and that long duration of anesthesia (odds ratio 2.51, $p < 0.001$) and the use of Pringle maneuver (odds ratio 1.37, $p = 0.007$) were independent risk factors of GI complications after hepatectomy. During the Pringle maneuver when vascular occlusion techniques are applied, the blood from the intestine and pancreas accumulated in the portal venous system leading to portal hypertension and gut congestion. Bowel wall edema may increase the intra-abdominal pressure and in turn deteriorate intestinal perfusion [11].

3.1.6 Intestinal Transplantation

Intestinal transplantation is a treatment option for irreversible intestinal failure. Both warm and cold ischemia phase insult the transplanted intestine directly for temporary interruption of blood supply. Then, the restoration of blood flow to the intestine graft causes oxidative stress and activates innate immunity leading to cell death [12].

3.1.7 Intestinal Diseases

Some disease directly insulting the intestine or intestinal vasculature can lead to intestinal ischemia, such as acute mesenteric thrombosis, mesenteric embolism, volvulus and neonatal necrotizing enterocolitis [13], etc. Symptoms of these diseases are often non-specific and can be subtle, resulting in a delay of correct diagnosis which decreases survival probability, especially when complicated with lung

injury and MOF. In infants with necrotizing enterocolitis, immature regulatory control of mesentery circulation makes the intestinal microvasculature vulnerable. The compromised vasculature increases circulation resistance and therefore decreases intestinal perfusion and may eventually progress to intestinal necrosis [14].

3.2 Mechanism of Perioperative Intestinal Injury

3.2.1 Intestine Barrier Function Impairment

The intestinal mucosal barrier consisted of mechanical barrier, immune barrier, chemical barrier, and microbiota barrier. Whether internal or external factors such as ischemia, hypoxia, infection, stress, etc. can impair these barrier functions, and these barrier function impairments often coexist with each other and have synergistic pathogenic effects.

3.2.1.1 Mechanical Barrier Function

Mechanical barrier function has a pivotal role in intestinal barrier functions. This role depends largely on the integrity of mucosal epithelial cells and tight junction between adjacent epithelial cells. Generally, the mechanical barrier function also includes intestine movement, intestinal epithelial cell cilia swing, and intestinal peristalsis, all of which can reduce the chance of pathogen adhesion to mucosal epithelial cells, preventing bacteria from staying in local intestinal mucosa for too long, just like intestinal self-cleaning. Mechanical barrier function impairment is characterized by increased intestinal mucosal permeability and epithelial cell damage such as cell necrosis, apoptosis, and ulceration. After exposure to the risk factors, blood redistribution occurs, and gut blood flow is drastically reduced in order to maintain important organ such as brain and heart blood supply, putting intestinal tract into ischemia, hypoxia, and acidosis state. Excessive oxyradical is produced by the gut, cellular metabolism disturbed by acidosis, and tissue injury induced. Simultaneously, extracellular calcium influx is triggered and intestinal mucosal epithelial edema aggravated. The epithelial cell membrane and intercellular junction rupture causes cell necrosis, ulceration, and increased intestinal mucosa permeability. On the other side, the intestinal tract can generate a large number of inflammatory mediators like nitric oxide, tumor necrosis factor, interleukin, interferon gamma, etc. under severe trauma, infection, and shock conditions. These inflammatory mediators interact with each other and form cascade reactions and then cause intestinal mucosa damage. Meanwhile, the reactive oxygen species (ROS) and inflammatory mediators produced by reperfusion subsequently can further damage the intestinal tract. When the body suffers trauma, chilliness, and pain, small intestine motility is inhibited through neurohumoral regulation resulting in prolonged bacterial retention and increased chance of colonization in the intestinal mucosa. Then, large amount of metabolite is produced by the implanted bacteria, and the gut mucosa structure damaged.

Reactive oxygen species are by-products of normal metabolism of cells, which can be beneficial to tissues at low and moderate doses by assisting wound healing, pathogen elimination, and tissue repair. Under pathological conditions like ischemia/reperfusion, excessive ROS is generated and causes oxidative damage to proteins and DNA and increased lipid peroxidation, leading to altered cell growth, differentiation, and apoptosis. Reperfusion-caused tissue damage is primary due to the reentry of oxygen rather than ischemia itself. It is explained by some researcher that ATP is metabolized into hypoxanthine during the ischemia period; when reperfusion starts, oxygen reacts with hypoxanthine to form xanthine and superoxide anion, large amount of oxygen-free radicals. Reperfusion enhances the ischemia injury by generating excessive ROS and accumulating activated neutrophils [15, 16].

Liu et al. built the animal model of intestinal ischemia/reperfusion injury by temporarily clamping and reopening the superior mesenchymal artery (SMA) in rats. Through animal experiment they found large amount of intestinal epithelial cell necrosis and apoptosis after intestine ischemia/reperfusion, and that intestinal injury could be improved by inhibiting cell apoptosis [17]. Based on these researches, it can be deduced that searching for important target of intestinal mucosal epithelial cell apoptosis regulation should be the key to prevent and treat intestinal I/R injury. Then, Wen et al. carried out a series of studies using the rat SMA occlusion/reopen model and demonstrated that aldose reductase, alpha-2 adrenergic receptor, and JAK2/STAT3 signaling were important molecules regulating intestinal mucosal epithelial cell apoptosis induced by intestinal ischemia/reperfusion [18]. In addition, Liu KX and his colleague described the microRNA expression profile during intestinal ischemia/reperfusion in rats for the first time and found that 19 microRNA expressions changed after I/R in intestinal mucosa, 1 upregulated and 18 downregulated including miRNA378. Through further studies of its function, they found upregulation of miRNA378 could reduce intestinal mucosal cell apoptosis and relieve gut injury [19].

Recent studies have shown that cell ischemic injury can cause not only apoptosis and necrosis but also another form of cell death, necroptosis, which morphologically looks like necrosis and apoptosis combined. Necroptosis is regulated by a series of signal pathways and metabolic mechanisms, except apoptosis-regulating factors such as caspase family, and is energy consuming. Wen et al. discovered that administrating necroptosis inhibitor Nec-1 could relieve gut ischemia/reperfusion injury in rats, and blocking both the apoptosis and necroptosis by using Nec-1 and Z-VAD (pan-caspase inhibitor) combined provided better intestinal protection. Our studies demonstrated that necroptosis played an important role in the mechanism of intestinal epithelial cell death after gut ischemia [17].

Tight junctions (TJ) are located at the apical lateral region of adjacent intestinal epithelial cells and composed of a group of transmembrane proteins such as claudins and occludins, as well as peripheral membrane proteins zonula occludens proteins (ZO-1-3). They play the major part of mechanical function of intestinal barriers by maintaining epithelial integrity, cellular polarity, and homeostasis and regulating the permeability of paracellular spaces in the epithelial mucosa [20–22]. Takizawa

et al. reported that damage of intestinal mucosa by intestinal I/R injury occurred with the start of reperfusion in a manner dependent on the severity of the lesion. Claudin-2 is an important factor for TJ construction and its remodeling. Claudin-4 regulates paracellular permeability in the intestine during intestinal ischemia/reperfusion [23, 24]. Chi et al. demonstrated that in a liver transplant-induced intestinal I/R model, occludin and ZO-1 expression in intestinal epithelia decreased, accompanied by elevated concentrations of D-LA, DAO, and FABP2 in serum, which suggested a compromised TJ structure leading to the epithelial barrier dysfunction [20]. Paracellular permeability across intestinal epithelium is largely regulated by the tight junctions. Increased intestinal permeability results in leakage of bacteria, microbial products, or other antigens from the intestinal lumen into the lamina propria to initiate or exacerbate an inflammatory response [21].

3.2.2 Immune Barrier Function

The intestinal immune barrier mainly consists of intestinal plasma cell secretory immunoglobulin (S-IgA), gut-associated lymphoid tissue (GALT), and liver defense function (gut-liver axis). These components work together to prevent pathogen invasion and injury to the gut and body through humoral and cellular immunity.

3.2.2.1 Humoral Immune Function Impairment

S-IgA is the main immune defense against luminal pathogens at intestinal mucosal surfaces. This defensive effect may be weakened by significantly inhibited intestinal S-IgA production, including lowered S-IgA content, S-IgA synthesizing plasma cell loss or dysfunction, and decreased S-IgA binding capacity to Gram-negative bacteria. The gut cannot maintain its resistance to bacterial colonization due to insufficient S-IgA production, and then intestinal bacteria translocation occurs. Zhang et al. reported that intestinal I/R resulted in impaired class switch recombination (CSR) of IgM B^+ cells, a key biological process involved in mucosal IgA synthesis, in Peyer's patches (PPs) and decreased secretory IgA concentration in the gut lumen 2 h after reperfusion [25]. Then they employed transforming growth factor β (TGF-β) to activate IgA CSR and promote IgA production in the intestinal tract of rats and demonstrated that TGF-β could improve gut IgA secretion and protect intestinal mucosal epithelial integrity against ischemia/reperfusion injury and lower the 24-h death rate of intestinal I/R rats [26]. S-IgA also has anti-inflammatory activities. It is reported that S-IgA can inhibit enterocyte apoptosis induced by ischemia/reperfusion and maintain mucosal integrity [27].

Natural immunoglobulin (Ig) M has been identified as one of contributors to I/R injury. Non-muscle myosin type II (NM-II) heavy chain A and C have been recognized as self-targets of natural IgM and IR injury in the small intestine of mice [28]. Ischemia-mediated aggregation of the actin cytoskeleton leads to the deposition of natural IgM and the activation of complement [29]. Reperfusion of the ischemic tissues shows an acute inflammatory response activated by natural IgM binding to ischemia-specific self-antigens, which are non-muscle myosin heavy chains type II

(NM-II) heavy chain subtype A and C. The natural IgM-antigen complexes combine with mannan-binding lectin (MBL) and activate the complement [28], a story part of the innate immune system which recognizes self-antigen and initiates inflammatory responses the way they encounter pathogens. Neoantigens or modified epitopes presented on the cell surface in ischemic tissues may also trigger complement activation via natural IgM deposition. Three pathways leading to the activation of the complement system have been identified: the classical, the lectin, and the alternative pathways. Each is activated by different initiators but all converge on C3 activation, which is followed by a common cascade. Lectin complement pathway operates immediately downstream of the natural IgM-ischemic antigen interaction during intestinal I/R. The classical complement pathway also appears to interact with the natural IgM-ischemic antigen immunocomplex. But the alternative complement pathway was not seen involved in I/R injury induction in the mice model [28]. Intracellular ROS formation and lipid peroxidation leads to an innate autoimmune response by natural IgM and complement [30]. It is reported that activation of complement C5a can deteriorate intestinal I/R-induced lung injury through autophagy-mediated alveolar macrophage apoptosis [31]. Inhibiting C5a activation significantly reduces the inflammatory cells such as polymorphonuclear leukocyte and macrophages near the injured site, increases proliferation of epithelial cells in the villi, and prevents further damage [32]. In addition, it is also reported that the ischemic tissue expresses a chemokine CXCL13 that attracts B cell, and accumulation of B cells contributes to the intestinal ischemia/reperfusion injury through an antibody-independent way [33].

Paneth cells are located at the base of the crypts of Lieberkühn (intestinal gland) and participate in the innate immune response by secreting several antimicrobial compounds including α-defensins and lysozyme into the gut lumen when exposed to bacteria or bacterial antigens. Because of its active secretory function, Paneth cell is vulnerable to endoplasmic reticulum (ER) stress which arises from a series of conditions including ischemia. Intestinal I/R results in activation of the unfolded protein response may also lead to Paneth cell apoptosis. Paneth cell dysfunction increases bacterial translocation and systemic inflammation in rats simultaneously with physical intestinal damage compared with rats with normal Paneth cell function [34].

3.2.2.2 Cellular Immune Function Impairment

Gut-associated lymphoid tissue (GALT) plays a central role in the systemic mucosal immune system; the reduction of GALT mass and function may disturb mucosal immunity. Lack of oral intake after gut I/R contributes to the reduction in GALT cell number [35] and also leads to intestinal mucosal T-cell dysfunction; hence, the mucosal resistance to infection is lowered. The goblet cell is insulted at the same time; its secretion of mucin is decreased, reducing the non-specific barrier function of gut mucosa. Severe infection, inflammation, and shock not only cause systemic immune dysfunction but also reduce lymphocyte in lamina propria and damage GALT. In addition, they also lower S-IgA secretion and induce Kupffer cell apoptosis and then destroy the intestinal mucosal immune barrier. Watson et al. used

anti-thymocyte globulin (ATG) to deplete T cells in a ischemia/reperfusion mice model and found that the MPO and proinflammatory factors such as tumor necrosis factor-α, interferon-γ, and interleukin-2 decreased with less local T-lymphocyte infiltration, and the epithelial cell apoptosis was also inhibited [36]. Regulatory T cells (Tregs), expressing CD4 and CD25, are a subset of T cells that modulate the immune system, maintain tolerance to self-antigen, and downregulate induction and proliferation of effector T cells. Partial depletion of Treg enhances secretion of tumor necrosis factor-α, interferon-γ, and interleukin (IL)-4 and increases intestinal permeability, while adapted transfer of Treg can reverse this effect [37].

Mast cells (MCs) constitute 2–3% of lamina propria cells; as a part of the immune system of the gut, they serve as first responders to invading pathogens and cellular stress signals. During intestinal ischemia/reperfusion, activated mast cells move to the tip of villus tip area and degranulate, releasing numerous inflammatory cytokines and causing tissue injury [38]. Intestinal ischemia/reperfusion may also activate macrophages, which then release cytokines, enhance myeloperoxidase activity, promote ROS production, and cause epithelial cell death [39]. Liu et al. reported that intestinal I/R injury caused a switch from M2 to M1 macrophages. Recombinant *Trichinella spiralis* cathepsin B-like protein (rTsCPB) could significantly relieve mucosal injury and improve intestinal function by promoting M1 to M2 macrophage phenotype transition. Inhibiting M1 to M2 transition could reverse the protective effects of rTsCPB. This study provided a potential choice of therapeutic agent that might be used in intestinal I/R injury [40]. Kupffer cells, the hepatic specific macrophages, are important sources of amplification of proinflammatory cytokine release such as TNF-α and IL-6 after intestinal ischemia, which in return aggravate intestinal injury [41].

3.2.3 Microbiota Barrier

The intestinal tract harbors the majority of microorganisms of the human body, up to 78% of total microbial populations, and 95% of the microbiota in gut are anaerobic bacteria. The anaerobic bacteria attach to the specific receptors on the epithelial cell surface forming microbial membrane structures, and they can restrain the pathogen colonization and proliferation and promote intestinal peristalsis and mucus flow. The intestinal resident bacteria and the host's intestine spatial microstructure are interdependent and interactive with each other; they form a relatively stable, multilayer microecosystem in the gut lumen, biologically antagonistic to pathogens. Microbiota activate the immune system in the gut and enhance the secretion of S-IgA and IgM. A relatively large portion of microbiota are coated with S-IgA, forming microbiota S-IgA complex, and help to maintain gut homeostasis. Free S-IgA upregulates expression of TNF-α, IL-8, and polymeric immunoglobulin receptor, whereas microbiota-complexed S-IgA ameliorates this effect [42]. When the balance between host and microflora or among different groups of microbiota was interrupted by exogenic factors, the intestinal biological barrier is impaired through the following mechanisms: First, followed by mechanical gut injury, the

intraluminal microflora enters submucosal tissue through the intestinal mucosa with increased permeability, leading to bacteria translocation, breaking the equilibrium of intestinal microbiota and the balance of gut microecosystem and then damaging intestinal biological barrier. Second, diminished bile secretion and intestinal-hepatic circulation disorder result in intestinal dysfunction and overgrowth of intestinal bacteria. Third, depressed peristalsis or oxygen uptake can lower intestinal metabolic rate and cause intestinal flora imbalance, G-bacteria overgrowth, and excessive production of endotoxin which can damage the intestinal mucosa.

Hoehn et al. reported that intestinal ischemia/reperfusion lead to bacterial overgrowth in the jejunum lumen and increases concentration of ceramide in the jejunal villi vasculature as well as the cell membrane of proliferated bacteria [43]. Ceramide has been demonstrated to be related to intestinal epithelial cell apoptosis, and antioxidative anesthetics like propofol and *Ginkgo biloba* extract can inhibit gut epithelium apoptosis via reducing ceramide production [44, 45]. Wang et al. used DGGE fingerprints to investigate the gut microbiota pattern changes after intestinal ischemia/reperfusion and figured out that *Escherichia coli* proliferation accompanied by *Lachnospiraceae* and *Lactobacilli* reduction was the characteristics of dysbiosis followed by intestinal I/R injury. Pattern changes of these three groups of bacteria are associated with increased proinflammatory factor secretion and pathogen adherence as well as decreased antimicrobial substances and tight junction assembly [46].

3.2.4 Chemical Barrier

The intestinal chemical barrier consists of mucus, digestive juice, and antimicrobial substance produced by intestinal microbiota. These components can dilute toxin, kill pathogenic bacteria, and combine with and limit the absorption of endotoxin. Mucus is mainly secreted by goblet cells, and intestinal ischemia/reperfusion significantly decreases goblet cell numbers in animal models [47]. In patients with severe infection or trauma, their intestinal mucosal renewal and repair ability is reduced by lacking stimulation of food and digestive hormone due to fasting. Meanwhile, the secretion of gastric acid, bile, lysozyme, and mucopolysaccharide decreased, weakening the chemical bactericidal ability of digestive juice. In some patient who underwent continuous gastrointestinal decompression, the bactericidal, toxin dilution and endotoxin combination ability decreased significantly due to gastric acid, bile, and pancreatic juice loss. In addition, drugs used to lower stomach acidity to prevent stress ulcer in critically ill patients can also weaken the chemical barrier function. It has been demonstrated that intestinal ischemia/reperfusion can cause gastrin dysfunction, inhibit basal acid secretion and weaken the acid secretory response to pentagastrin, and induce accumulation of alkalized gastric fluid rich in glucose, protein, and bicarbonate [48]. Liu et al. reported that elevated serum gastrin concentration could ameliorate epithelial disruption, decrease disintegration of lamina propria, reduce proinflammatory factor production that inhibits apoptosis, and lower mortality in intestinal I/R rat models [49]. Mucin, the major protein of mucus, is disrupted during the early phase of ischemia [50]. I/R insult leads to oxidative modification

and extrusion of the mucus layer into the intestinal lumen, and the mucus is further degraded by pancreatic proteases; the thinned and degraded mucus layer allows pancreatic proteases and bacteria to cross the epithelium line and enter the submucosal space and triggers inflammatory response [51]. Qin et al. reported that treatment of the gut with the mucolytic NAC during ischemia could enhance mucosal permeability and aggravate gut injury and that the presence of digestive proteases by themselves did not exacerbate gut injury, but in combination with NAC, they induced an even greater increase in intestinal permeability and injury [52]. Grootjans et al. reported that intestinal ischemia lead to mucus layer detachment in the colon and bacteria penetration to the mucosa, while increasing secretory activity of goblet cells could expulse the bacteria out of the crypts and restore mucus layer [53].

3.2.5 Remote Organ Damage Due to Intestinal Injury

Impaired intestinal barrier function leads to bacteria and endotoxin translocation and activates the monocyte/macrophage system to release a large number of inflammatory mediators and cytokines, resulting in systemic inflammation and even multiple organ dysfunction syndrome and multiple organ failure. Lung and heart injuries after intestinal I/R, the second hit, are an important prognostic factor for patient survival. Patients who underwent cardiopulmonary bypass or abdominal aortic aneurysm surgery often experienced cognitive dysfunction, suggesting that they may have concomitant brain injury. To clarify whether their brain injury was associated to intestinal I/R or not, Zhou and Liu et al. built an intestinal I/R injury model in rats and found that intestinal I/R could induce brain edema and cerebral cortex and hippocampus damage in rats, accompanied by reduced memory and spatial learning capacity, as well as decreased survival rate of the animals. Further studies demonstrated that microglia activation aggravated inflammation response and oxidative stress injury in the brain tissue and promote neuronal cell apoptosis. It may be the major part of the mechanism of intestinal I/R-induced brain damage and memory dysfunction. Liu et al. investigations suggest that close attention should be given to cognitive dysfunction manifestations of patients with intestine I/R risk factors [54]. In addition, beta-defensin-2 is one of the endogenous protective factors in the human body, and it is one of the main factors for the body to resist exogenous stimuli. Liu et al. found that I/R upregulated both gene and protein expression of beta-defensin-2 in rats. The expression of beta-defensin-2 was related to the activation of inflammatory cytokines in the lung, and when its expression was upregulated in the lung, it could significantly improve pulmonary injury caused by intestinal I/R [55].

3.3 Prevention and Treatment

Many explorations of the strategy to prevent intestinal barrier injury have been made in the recent years as the knowledge on intestinal mucosal barrier functions deepens. Numerous regimen and therapies have been reported to be efficacious in

preventing or treating intestinal ischemia/reperfusion injury in experimental animal studies. The vast majority of animal model used in these studies was the mouse/rat model established by temporarily clamping and reopening of the superior mesenteric artery. However, the treatment options available for intestinal ischemia/reperfusion injury in the clinical settings are still limited.

3.3.1 Early Enteral Nutrition

Early enteral nutrition (EN) support is the primary measure to protect the intestinal mucosal barrier function; it can prevent intestinal mucosal atrophy and reduce intestinal bacterial translocation. It also stimulates gastrointestinal hormone release, promotes gut peristalsis, and brings quicker recovery of intestinal barrier function. Enteral nutrition with addition of arginine, polyunsaturated fatty acids, nucleotides, vitamin A, and glutamine facilitates this process. Lin et al. reported that both conventional and lipid-rich EN via gavage increased the intestinal motility and the intestinal mucosal tight junction protein expression and decreased the serum I-FABP levels and reduced systemic inflammatory response after intestinal I/R injury in rats, while lipid-rich EN conferred better effects in controlling intestinal inflammation and improving mucosal barrier function than conventional EN did [56]. Wu et al. demonstrated that 20% dose of enteral nutrition had a significantly better protective effect than total parenteral nutrition did on intestinal barrier function in rat II/R model [57].

3.3.1.1 Glutamine (Gln)

Glutamine is the main energy source of intestinal epithelium and essential nutrient for intestinal mucosa metabolism and regeneration. It is also the precursor of reduced glutathione, an important component of the cellular antioxidant system. Under severe stress conditions, glutamine demand will exceed its production; deficiency of Gln will lead to atrophy of intestinal mucosa, thinning of villi, and impaired intestinal barrier function. Extra-enteral nutrition with proper supplementation of glutamine or enteral nutrition can increase intestinal villus height, reduce intestinal mucosal permeability and enhance intestinal immunity, prevent bacterial translocation, and then maintain intestinal mucosal barrier function. Shu et al. reported that rats fed with vegan chow with 3% Gln supplementation exerted beneficial anti-inflammatory effect and improved morphological changes in the gut mucosa after intestinal ischemia/reperfusion [58]. It is also found that peroxisome proliferator-activated receptor gamma (PPARγ), a member of the nuclear receptor superfamily of transcription factors which is highly expressed in intestinal epithelium, played a pivotal role in enteral Gln's protection to the postischemic gut [59].

3.3.1.2 Growth Factors

Epidermal growth factor (EGF) plays an important role in the growth, differentiation, and tissue repair of intestinal epithelial cells. It can increase the synthesis of glutamine in the body and promote the absorption and utilization of glutamine in the

intestine and has a synergistic effect with glutamine on the intestinal tract. It has been found that EGF can reduce intestinal bacterial translocation and lower mortality rate in patient subject to total parenteral nutrition. Insulin-like growth factor (IGF) is synthesized by liver cells and contributes to cell division. Animal studies have shown that it can increase DNA and protein synthesis in intestinal mucosal cells, restrain intestinal mucosal atrophy and barrier destruction, and reduce the mortality rate of infection.

3.3.2 Anti-oxyradical Agent

The intestine is rich in xanthine oxidase (XOD), which produces oxygen-free radicals (OFR) under hypoxia or ischemic conditions. Excessive OFR causes intestinal mucosa damage but can be antagonized by exogenous or exogenous OFR scavengers. Selenium is an essential trace element known to have an antioxidant effect as a critical cofactor for the function of glutathione peroxidase, which is involved in the oxidation of glutathione. Kim et al. reported that selenium treatment might protect the intestine by increasing glutathione peroxidase activity, reducing lipid peroxidation, and downregulating the NF-κB pathway during intestinal I/R injury in rats [60]. Trapidil is a phosphodiesterase and platelet-derived growth factor inhibitor. Colak et al. demonstrated that trapidil treatment could protect intestinal barrier function in rat intestinal I/R model via inhibiting lipid peroxidation, improving nitric oxide metabolism, and suppressing thromboxane A2 and proinflammatory cytokine production [61, 62]. Melatonin is an endogenous hormone secreted by the pineal gland and has strong anti-oxidative effect; pretreating melatonin or its natural intermediate product, N-acetylserotonin, can attenuate intestinal I/R-induced intestinal and lung injuries [63–65]. Pyruvate has been proved to be a potent ROS scavenger, directly neutralizing peroxides and peroxynitrite and also scavenging hydroxyl radicals. Pyruvate-peritoneal dialysis solution (PDS) following intravenous resuscitation improves intestinal barrier function in rats with hemorrhagic shock through eliminating free oxygen radicals, reducing neutrophil infiltration, and inhibiting inflammatory response [66, 67]. Resveratrol is a natural phytoalexin found in dietary sources such as grapes, plums, peanuts, and wine. Accumulating evidence indicates that resveratrol may have therapeutic potential for intestinal I/R injury by its antioxidant, anti-inflammatory, and antiapoptotic properties [68]. Resveratrol treatment yields effects of protecting myenteric neurons and limiting enteric glial cell proliferation in the ileum, alleviating lung injury via suppressing mast cell degranulation in intestinal I/R rats [69, 70].

3.3.3 Traditional Chinese Medicine

The traditional Chinese medicine (TCM) differentiation theory attributes microcirculation disorders in early intestinal ischemia/reperfusion to poor blood supply and blood stasis, and many medications were developed under this theory. Xuesaitong

injections, whose major component is panax notoginseng saponins, the active ingredient of notoginseng plant, are widely used prior to clinical procedures. Xu et al. reported that intraperitoneal injection of Xuesaitong once a day for a week prior to ischemia improved gut peristalsis and reduced intestinal mucosal apoptosis after reperfusion in the IRI rat model [71]. Jiang et al. demonstrated that ginsenoside Rb1 could alleviate lung histological injury, suppress inflammatory responses, and reduce tissue edema by activating nuclear factor erythroid 2-related factor-2 (Nrf2)/heme oxygenase-1(HO-1) pathway in mice model of intestinal I/R-induced lung injury [72]. Qinghuobaiduyin (QHBDY) is a traditional Chinese medicine that has been used to treat burn patients for more than 20 years. Zhu et al. demonstrated QHBDY reduced intestinal epithelial cell apoptosis following burn at both animal and cellular levels [73]. Mo et al. reported that osthole, a component of a traditional Chinese medicine fructus cnidii extract, could inhibit inflammatory response and oxidative stress and attenuate the lung injury induced by II/R in rats [74].

3.3.4 Anesthetics

It has been demonstrated that commonly used anesthetics, like propofol, remifentanil, and dexmedetomidine, can attenuate intestinal I/R-induced intestinal injury. The gut protection effect of these drugs might be related to their antioxidant properties reducing lipid peroxidation and attenuation of apoptosis of intestinal epithelial cells [44, 45, 75, 76]. Gan et al. reported that propofol could inhibit intestinal I/R--induced NADPH oxidase overexpression and suppress ROS-mediated mast cell degranulation [77]. The suppression of ROS and mast cell activation by propofol can also alleviate lung injury induced by intestinal I/R [78]. Gan et al. found that rats exposed to 2.3% sevoflurane for 1 h for 3 subsequent days prior to ischemia/reperfusion procedure showed reduced inflammation and increased SOD activities in the intestinal mucosa as well as improved postischemic survival rate possibly by inhibiting oxidative stress in a mast cell-independent way [79]. Liu et al. demonstrated that pretreatment with 0.5 MAC sevoflurane inhalation in intestinal I/R rat model attenuated gut injury by inhibiting intestinal mucosal epithelial apoptosis via activation of the PI3K/Akt pathway [80]. Kim et al. showed that 4 h of 1MAC isoflurane inhalation after intestinal ischemia led to inhibited epithelial cell apoptosis, alleviated intestinal injury, and improved renal and hepatic dysfunction by induction of intestinal epithelial TGF-beta1 [81]. Shen et al. conducted remifentanil pretreatment in rat model using three cycles of 5 min of remifentanil infusion alternating with 5 min of normal saline before ischemia and found that remifentanil pretreatment inhibited intestinal epithelial cell apoptosis and ameliorated histological injury. The protective effect was dose independent within the range of 0.2–1 mg kg^{-1} min^{-1} RF and was achieved by acting via intestinal delta- and mu-opioid receptors [75]. Dexmedetomidine is a potent and highly selective α2 adrenoreceptor agonist widely used in clinical anesthesia. It has also been demonstrated to have anti-inflammatory and organ protective effects. Zhang et al. reported that dexmedetomidine administration before ischemia at a dose of 5 μg kg^{-} h^{-} in rats, which

is equal to 0.8 μg kg^{-} h^{-} in humans, attenuated intestinal ischemia/reperfusion injury partly by inhibiting inflammatory response and intestinal mucosal epithelial apoptosis via activating the α2-adrenoceptors [76].

3.3.5 Antiendotoxin Therapy

Endotoxins are the major components of the outer membrane of most Gram-negative bacteria [82]. Endotoxin can be removed by peritoneal lavage, hemodialysis, or activated carbon adsorption. Whole-bowel irrigation can reduce the number of intestinal flora and drastically decrease the amount of the absorbable endotoxin pool in the gut. Selective decontamination of digestive tract (SDD) can be used to inhibit the production of intestinal endotoxin by diminishing the number of Gram-negative bacilli in the intestinal tract. The widely used SDD regimen is PTA (polymyxin E, tobramycin, and amphotericin B) in clinical settings. Lactulose, a nontoxic synthetic disaccharide, reduces endotoxin absorption by reducing or altering the intestinal flora. Oral application of lactulose can prevent or eliminate systemic endotoxemia.

3.3.6 Ischemic Preconditioning/Postconditioning

Ischemic preconditioning is a physiologic mechanism by which tissues and organs exposed to a short period of ischemia/reperfusion(I/R) prior can develop resistance to ischemic insults and significantly attenuate intestinal injury by inhibiting the neutrophil-endothelial adhesion cascade via reducing ICAM-1 and VCAM-1 expression and TNF-α-induced NF-κB signaling pathway [83]. However, organ ischemia episodes are often unpredictable, and the actual treatment can only be applied afterward. Considering the limitations of preconditioning, here comes a more clinically feasible concept of ischemic postconditioning that reperfusion or ischemia treatment is performed immediately after the initial longer period of ischemia/reperfusion insult. It was found that myocardial I/R damage can be significantly reduced by postconditioning treatment. Liu et al. have done a series of investigations to explore the gut protection effect and mechanism of ischemic postconditioning in intestinal I/R rats. Their discoveries are as follows. First, ischemic preconditioning and postconditioning have similar protective effect against intestinal and lung injury induced by intestinal I/R in rats, and their effects can be synergistic. Second, if the postconditioning treatment were not applied until 3 min after reperfusion (i.e., delayed treatment), the protective effect of postconditioning disappeared, suggesting that the protective effect have a time window and ischemic postconditioning treatment should be carried out within this period in clinical practice. Third, both ischemic preconditioning and postconditioning play a role in intestinal protection by upregulating the expression of aldose reductase and inhibiting intestinal mucosal cell apoptosis, and aldose reductase is the common target. Fourth, postconditioning treatment inhibits intestinal mucosal cell apoptosis by inhibiting

JAK2/STAT3 pathway [18, 84, 85]. Postconditioning also downregulates the transcription of Toll-like receptor 4 (TLR-4) mRNA, reduces protein expression of high-mobility group box-1 (HMGB-1) and TLR-4 in the intestinal mucosa, and inhibits cell apoptosis and inflammatory response [86]. Besides the unpredictability of ischemic episode, preconditioning itself has another limitation. It might deteriorate organ function or cause complications, such as plaque embolization, especially when arteries are intermittently occluded. Recently, a more clinically applicable stimulus is afforded by remote ischemic preconditioning (RIPC), which has been noted that a brief I/R in distant tissues, usually skeletal muscle, may bring the same protection effect in the heart. However, this method had not been reported to improve the long-term outcome of the patient, neither its role in intestinal I/R injury had been demonstrated. Li et al. evaluated the effect of limb RIPC in providing intestinal and pulmonary protection after elective open infrarenal abdominal aortic aneurysm (AAA) repair in a single-center, prospective, double-blinded, randomized, parallel-controlled trial. During the trial, it was demonstrated that intermittent upper limb ischemia as a RIPC stimulus conferred potential intestinal and pulmonary protection during elective open infrarenal AAA repair and significantly improved bowel and lung function while reducing postoperative hospital stay at ICU [87].

3.3.7 Stem Cell

Stem cells are undifferentiated biological cells and have the potential to differentiate into specified cells in specific organs and tissues. In humans, stem cells can be divided into two broad types: embryonic stem cells and adult stem cells. Stem cell therapy has gained much attention from researcher and physicians; many studies have shown encouraging effect from stem cell treatment. Because of ethical concerns, adult stem cells are the overwhelming majority of stem cell sources in these studies. Bone marrow stem cells can migrate, colonize, and differentiate into specific injured organs in vivo to accelerate the repair of damaged tissues. In many animal experiments and clinical studies, exogenous stem cell transplantation had been used in the treatment of intestinal injury. Shen et al. reported that bone marrow transplantation protected intestinal mucosal barrier function against intestinal I/R injury by inhibiting ZO-1 downregulation and tight junction disruption [88]. Adipose-derived mesenchymal stem cells (ASCs) show greater proliferative potential than bone marrow stem cells, and their easier accessibility and limitless supply via liposuction of subcutaneous adipose tissue make them an ideal candidate for widespread therapeutic use. Jensen et al. demonstrated that human adipose-derived stromal cell treatment improved 7-day survival and mesenteric perfusion and attenuated the mucosal damage associated with intestinal I/R injury in rats [89]. They also discovered that human umbilical cord-derived mesenchymal stem cells (MSC) and bone marrow-derived MSCs yielded the same effect on improving survival rate of intestinal I/R rats [90]. Chang et al. reported that combined melatonin and adipose-derived mesenchymal stem cell treatment conferred additive beneficial effect against intestinal IR injury and was superior to either alone [91].

3.4 Conclusion

With the development of surgical operations, how to effectively protect the organs during the perioperative period has become a major field of surgery studies, and it is of great significance to improve the success rate of surgical treatment. But at present our clinical study on perioperative intestinal injury is still facing some difficulties, such as (1) an ideal clinical model is still lacking; (2) there is no uniform bowel dysfunction evaluation standard; and (3) the symptoms of intestinal injury itself are often concealed by that of parenteral organ dysfunction caused by intestinal injury. Therefore, the clinical study of perioperative intestinal injury will be a difficult and long-term process. We anesthesiologists must recognize the harmful consequences of perioperative intestinal injury and do our utmost to improve patients' eventual outcomes.

References

1. Zhao L, Luo L, Chen J, Xiao J, Jia W, Xiao Y. Utilization of extracorporeal membrane oxygenation alleviates intestinal ischemia-reperfusion injury in prolonged hemorrhagic shock animal model. Cell Biochem Biophys. 2014;70(3):1733–40. https://doi.org/10.1007/s12013-014-0121-3.
2. Slone EA, Fleming SD. Membrane lipid interactions in intestinal ischemia/reperfusion-induced injury. Clin Immunol. 2014;153(1):228–40. https://doi.org/10.1016/j.clim.2014.04.018.
3. Oldenburg W, Lau L, Rodenberg T, Edmonds H, Burger C. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164(10):1054–62.
4. Smit M, Buddingh KT, Bosma B, Nieuwenhuijs VB, Hofker HS, Zijlstra JG. Abdominal compartment syndrome and intra-abdominal ischemia in patients with severe acute pancreatitis. World J Surg. 2016;40(6):1454–61. https://doi.org/10.1007/s00268-015-3388-7.
5. Tian R, Tan JT, Wang RL, Xie H, Qian YB, Yu KL. The role of intestinal mucosa oxidative stress in gut barrier dysfunction of severe acute pancreatitis. Eur Rev Med Pharmacol Sci. 2013;17(3):349–55.
6. Yang R, Tenhunen J, Tonnessen TI. HMGB1 and histones play a significant role in inducing systemic inflammation and multiple organ dysfunctions in severe acute pancreatitis. Int J Inflamm. 2017;2017:1817564. https://doi.org/10.1155/2017/1817564.
7. De Silva RJ, Bhinda P, Goddard M, Choong CK. The value of post mortems in cardiac surgery: learning from the dead. Heart Lung Circ. 2012;21(3):150–3. https://doi.org/10.1016/j.hlc.2011.11.005.
8. Adamik B, Kubler A, Gozdzik A, Gozdzik W. Prolonged cardiopulmonary bypass is a risk factor for intestinal ischaemic damage and endotoxaemia. Heart Lung Circ. 2017;26(7):717–23. https://doi.org/10.1016/j.hlc.2016.10.012.
9. Ultee KH, Zettervall SL, Soden PA, Darling J, Bertges DJ, Verhagen HJ, Schermerhorn ML. Incidence of and risk factors for bowel ischemia after abdominal aortic aneurysm repair. J Vasc Surg. 2016;64(5):1384–91. https://doi.org/10.1016/j.jvs.2016.05.045.
10. Li BC, Xia ZQ, Li C, Liu WF, Wen SH, Liu KX. The incidence and risk factors of gastrointestinal complications after hepatectomy: a retrospective observational study of 1329 consecutive patients in a single center. J Surg Res. 2014;192(2):440–6. https://doi.org/10.1016/j.jss.2014.06.015.
11. Nastos C, Kalimeris K, Papoutsidakis N, Tasoulis MK, Lykoudis PM, Theodoraki K, et al. Global consequences of liver ischemia/reperfusion injury. Oxidative Med Cell Longev. 2014;2014:906965. https://doi.org/10.1155/2014/906965.

12. Lenaerts K, Ceulemans LJ, Hundscheid IH, Grootjans J, Dejong CH, Olde Damink SW. New insights in intestinal ischemia-reperfusion injury: implications for intestinal transplantation. Curr Opin Organ Transplant. 2013;18(3):298–303. https://doi.org/10.1097/MOT.0b013e32835ef1eb.
13. Zhang HY, Wang F, Feng JX. Intestinal microcirculatory dysfunction and neonatal necrotizing enterocolitis. Chin Med J. 2013;126(9):1771–8.
14. Neu J. Necrotizing enterocolitis. World Rev Nutr Diet. 2014;110:253–63. https://doi.org/10.1159/000358474.
15. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev. 2014;94(2):329–54. https://doi.org/10.1152/physrev.00040.2012.
16. Mallick IH, Yang W, Winslet MC, Seifalian AM. Ischemia-reperfusion injury of the intestine and protective strategies against injury. Dig Dis Sci. 2004;49(9):1359–77.
17. Wen S, Ling Y, Yang W, Shen J, Li C, Deng W, et al. Necroptosis is a key mediator of enterocytes loss in intestinal ischaemia/reperfusion injury. J Cell Mol Med. 2017;21(3):432–43. https://doi.org/10.1111/jcmm.12987.
18. Wen SH, Li Y, Li C, Xia ZQ, Liu WF, Zhang XY, et al. Ischemic postconditioning during reperfusion attenuates intestinal injury and mucosal cell apoptosis by inhibiting JAK/STAT signaling activation. Shock. 2012;38(4):411–9. https://doi.org/10.1097/SHK.0b013e3182662266.
19. Li Y, Wen S, Yao X, Liu W, Shen J, Deng W, et al. MicroRNA-378 protects against intestinal ischemia/reperfusion injury via a mechanism involving the inhibition of intestinal mucosal cell apoptosis. Cell Death Dis. 2017;8(10):e3127. https://doi.org/10.1038/cddis.2017.508.
20. Chi X, Yao W, Xia H, Jin Y, Li X, Cai J, Hei Z. Elevation of HO-1 expression mitigates intestinal ischemia-reperfusion injury and restores tight junction function in a rat liver transplantation model. Oxidative Med Cell Longev. 2015;2015:986075. https://doi.org/10.1155/2015/986075.
21. Jin Y, Blikslager AT. Myosin light chain kinase mediates intestinal barrier dysfunction via occludin endocytosis during anoxia/reoxygenation injury. Am J Physiol Cell Physiol. 2016;311(6):C996–c1004. https://doi.org/10.1152/ajpcell.00113.2016.
22. Wells JM, Brummer RJ, Derrien M, MacDonald TT, Troost F, Cani PD, et al. Homeostasis of the gut barrier and potential biomarkers. Am J Physiol Gastrointest Liver Physiol. 2017;312(3):G171–g193. https://doi.org/10.1152/ajpgi.00048.2015.
23. Takizawa Y, Kishimoto H, Kitazato T, Tomita M, Hayashi M. Changes in protein and mRNA expression levels of claudin family after mucosal lesion by intestinal ischemia/reperfusion. Int J Pharm. 2012;426(1–2):82–9. https://doi.org/10.1016/j.ijpharm.2012.01.023.
24. Takizawa Y, Kishimoto H, Tomita M, Hayashi M. Changes in the expression levels of tight junction components during reconstruction of tight junction from mucosal lesion by intestinal ischemia/reperfusion. Eur J Drug Metab Pharmacokinet. 2014;39(3):211–20. https://doi.org/10.1007/s13318-013-0151-z.
25. Zhang XY, Liu ZM, Zhang HF, Li YS, Wen SH, Shen JT, Liu KX. Decreased PD-1/PD-L1 expression Is associated with the reduction in mucosal immunoglobulin A in mice with intestinal ischemia reperfusion. Dig Dis Sci. 2015;60(9):2662–9. https://doi.org/10.1007/s10620-015-3684-y.
26. Zhang XY, Liu ZM, Zhang HF, Li YS, Wen SH, Shen JT, et al. TGF-beta1 improves mucosal IgA dysfunction and dysbiosis following intestinal ischaemia-reperfusion in mice. J Cell Mol Med. 2016;20(6):1014–23. https://doi.org/10.1111/jcmm.12789.
27. Diebel LN, Liberati DM, Dulchavsky SA, Diglio CA, Brown WJ. Enterocyte apoptosis and barrier function are modulated by SIgA after exposure to bacteria and hypoxia/reoxygenation. Surgery. 2003;134(4):574–80. https://doi.org/10.1016/s0039. discussion 580-571.
28. Lee H, Green DJ, Lai L, Hou YJ, Jensenius JC, Liu D, et al. Early complement factors in the local tissue immunocomplex generated during intestinal ischemia/reperfusion injury. Mol Immunol. 2010;47(5):972–81. https://doi.org/10.1016/j.molimm.2009.11.022.
29. Shi T, Moulton VR, Lapchak PH, Deng GM, Dalle Lucca JJ, Tsokos GC. Ischemia-mediated aggregation of the actin cytoskeleton is one of the major initial events resulting in ischemia-

reperfusion injury. Am J Physiol Gastrointest Liver Physiol. 2009;296(2):G339–47. https://doi.org/10.1152/ajpgi.90607.2008.
30. Zhang M, Alicot E, Carroll M. Human natural IgM can induce ischemia/reperfusion injury in a murine intestinal model. Mol Immunol. 2008;45(15):4036–9.
31. Hu R, Chen ZF, Yan J, Li QF, Huang Y, Xu H, et al. Complement C5a exacerbates acute lung injury induced through autophagy-mediated alveolar macrophage apoptosis. Cell Death Dis. 2014;5:e1330. https://doi.org/10.1038/cddis.2014.274.
32. Tuboly E, Futakuchi M, Varga G, Erces D, Tokes T, Meszaros A, et al. C5a inhibitor protects against ischemia/reperfusion injury in rat small intestine. Microbiol Immunol. 2016;60(1):35–46. https://doi.org/10.1111/1348-0421.12338.
33. Chen J, Crispin JC, Tedder TF, Dalle Lucca J, Tsokos GC. B cells contribute to ischemia/reperfusion-mediated tissue injury. J Autoimmun. 2009;32(3–4):195–200. https://doi.org/10.1016/j.jaut.2009.02.021.
34. Grootjans J, Hodin CM, de Haan JJ, Derikx JP, Rouschop KM, Verheyen FK, et al. Level of activation of the unfolded protein response correlates with Paneth cell apoptosis in human small intestine exposed to ischemia/reperfusion. Gastroenterology. 2011;140(2):529–539. e523. https://doi.org/10.1053/j.gastro.2010.10.040.
35. Fukatsu K, Sakamoto S, Hara E, Ueno C, Maeshima Y, Matsumoto I, et al. Gut ischemia-reperfusion affects gut mucosal immunity: a possible mechanism for infectious complications after severe surgical insults. Crit Care Med. 2006;34(1):182–7.
36. Watson MJ, Ke B, Shen XD, Gao F, Busuttil RW, Kupiec-Weglinski JW, Farmer DG. Treatment with antithymocyte globulin ameliorates intestinal ischemia and reperfusion injury in mice. Surgery. 2012;152(5):843–50. https://doi.org/10.1016/j.surg.2012.03.001.
37. Yang X, Bai H, Wang Y, Li J, Zhou Q, Cai W, et al. Deletion of regulatory T cells supports the development of intestinal ischemia-reperfusion injuries. J Surg Res. 2013;184(2):832–7. https://doi.org/10.1016/j.jss.2013.05.014.
38. Karhausen J, Qing M, Gibson A, Moeser AJ, Griefingholt H, Hale LP, et al. Intestinal mast cells mediate gut injury and systemic inflammation in a rat model of deep hypothermic circulatory arrest. Crit Care Med. 2013;41(9):e200–10. https://doi.org/10.1097/CCM.0b013e31827cac7a.
39. Chen Y, Lui VC, Rooijen NV, Tam PK. Depletion of intestinal resident macrophages prevents ischaemia reperfusion injury in gut. Gut. 2004;53(12):1772–80. https://doi.org/10.1136/gut.2003.034868.
40. Liu WF, Wen SH, Zhan JH, Li YS, Shen JT, Yang WJ, et al. Treatment with recombinant trichinella spiralis cathepsin B-like protein ameliorates intestinal ischemia/reperfusion injury in mice by promoting a switch from M1 to M2 macrophages. J Immunol. 2015;195(1):317–28. https://doi.org/10.4049/jimmunol.1401864.
41. Towfigh S, Heisler T, Rigberg DA, Hines OJ, Chu J, McFadden DW, Chandler C. Intestinal ischemia and the gut-liver axis: an in vitro model. J Surg Res. 2000;88(2):160–4. https://doi.org/10.1006/jsre.1999.5767.
42. Salerno-Goncalves R, Safavie F, Fasano A, Sztein MB. Free and complexed-secretory immunoglobulin A triggers distinct intestinal epithelial cell responses. Clin Exp Immunol. 2016;185(3):338–47. https://doi.org/10.1111/cei.12801.
43. Hoehn RS, Seitz AP, Jernigan PL, Gulbins E, Edwards MJ. Ischemia/reperfusion injury alters sphingolipid metabolism in the gut. Cell Physiol Biochem. 2016;39(4):1262–70. https://doi.org/10.1159/000447831.
44. Liu KX, Chen SQ, Huang WQ, Li YS, Irwin MG, Xia Z. Propofol pretreatment reduces ceramide production and attenuates intestinal mucosal apoptosis induced by intestinal ischemia/reperfusion in rats. Anesth Analg. 2008;107(6):1884–91. https://doi.org/10.1213/ane.0b013e3181884bbf.
45. Liu KX, He W, Rinne T, Liu Y, Zhao MQ, Wu WK. The effect of ginkgo biloba extract (EGb 761) pretreatment on intestinal epithelial apoptosis induced by intestinal ischemia/reperfusion in rats: role of ceramide. Am J Chin Med. 2007;35(5):805–19. https://doi.org/10.1142/s0192415x07005284.

46. Wang F, Li Q, He Q, Geng Y, Tang C, Wang C, Li J. Temporal variations of the ileal microbiota in intestinal ischemia and reperfusion. Shock. 2013;39(1):96–103. https://doi.org/10.1097/SHK.0b013e318279265f.
47. Ozkan O, Ozkan O, Bektas G, Cinpolat A, Bassorgun I, Ciftcioglu A. The relationship between ischemia time and mucous secretion in vaginal reconstruction with the jejunal free flap: an experimental study on the rat jejunum. Ann Plast Surg. 2015;75(1):98–101. https://doi.org/10.1097/01.SAP.0000466781.69925.b2.
48. Castaneda A, Vilela R, Chang L, Mercer DW. Effects of intestinal ischemia/reperfusion injury on gastric acid secretion. J Surg Res. 2000;90(1):88–93. https://doi.org/10.1006/jsre.2000.5853.
49. Liu Z, Luo Y, Cheng Y, Zou D, Zeng A, Yang C, et al. Gastrin attenuates ischemia-reperfusion-induced intestinal injury in rats. Exp Biol Med (Maywood). 2016;241(8):873–81. https://doi.org/10.1177/1535370216630179.
50. Chang M, Alsaigh T, Kistler EB, Schmid-Schonbein GW. Breakdown of mucin as barrier to digestive enzymes in the ischemic rat small intestine. PLoS One. 2012;7(6):e40087. https://doi.org/10.1371/journal.pone.0040087.
51. Fishman JE, Sheth SU, Levy G, Alli V, Lu Q, Xu D, et al. Intraluminal nonbacterial intestinal components control gut and lung injury after trauma hemorrhagic shock. Ann Surg. 2014;260(6):1112–20. https://doi.org/10.1097/SLA.0000000000000631.
52. Qin X, Sheth SU, Sharpe SM, Dong W, Lu Q, Xu D, Deitch EA. The mucus layer is critical in protecting against ischemia-reperfusion-mediated gut injury and in the restitution of gut barrier function. Shock. 2011;35(3):275–81. https://doi.org/10.1097/SHK.0b013e3181f6aaf1.
53. Grootjans J, Hundscheid IH, Lenaerts K, Boonen B, Renes IB, Verheyen FK, et al. Ischaemia-induced mucus barrier loss and bacterial penetration are rapidly counteracted by increased goblet cell secretory activity in human and rat colon. Gut. 2013;62(2):250–8. https://doi.org/10.1136/gutjnl-2011-301956.
54. Zhou J, Huang WQ, Li C, Wu GY, Li YS, Wen SH, et al. Intestinal ischemia/reperfusion enhances microglial activation and induces cerebral injury and memory dysfunction in rats. Crit Care Med. 2012;40(8):2438–48. https://doi.org/10.1097/CCM.0b013e3182546855.
55. Liu KX, Chen SQ, Zhang H, Guo JY, Li YS, Huang WQ. Intestinal ischaemia/reperfusion upregulates beta-defensin-2 expression and causes acute lung injury in the rat. Injury. 2009;40(9):950–5. https://doi.org/10.1016/j.injury.2009.01.103.
56. Lin ZL, Tan SJ, Cheng MH, Zhao CY, Yu WK, He YL, et al. Lipid-rich enteral nutrition controls intestinal inflammation, improves intestinal motility and mucosal barrier damage in a rat model of intestinal ischemia/reperfusion injury. J Surg Res. 2017;213:75–83. https://doi.org/10.1016/j.jss.2017.02.007.
57. Wu C, Wang X, Jiang T, Li C, Zhang L, Gao X, et al. Partial enteral nutrition mitigated ischemia/reperfusion-induced damage of rat small intestinal barrier. Nutrients. 2016;8(8):502. https://doi.org/10.3390/nu8080502.
58. Shu X, Zhang J, Wang Q, Xu Z, Yu T. Glutamine decreases intestinal mucosal injury in a rat model of intestinal ischemia-reperfusion by downregulating HMGB1 and inflammatory cytokine expression. Exp Ther Med. 2016;12(3):1367–72. https://doi.org/10.3892/etm.2016.3468.
59. Peng Z, Ban K, Wawrose RA, Gover AG, Kozar RA. Protection by enteral glutamine is mediated by intestinal epithelial cell peroxisome proliferator-activated receptor-gamma during intestinal ischemia/reperfusion. Shock. 2015;43(4):327–33. https://doi.org/10.1097/shk.0000000000000297.
60. Kim Y, Kim DC, Cho ES, Ko SO, Kwon WY, Suh GJ, Shin HK. Antioxidant and anti-inflammatory effects of selenium in oral buccal mucosa and small intestinal mucosa during intestinal ischemia-reperfusion injury. J Inflamm (Lond). 2014;11(1):36. https://doi.org/10.1186/s12950-014-0036-1.
61. Colak T, Ozturk C, Polat A, Bagdatoglu O, Kanik A, Turkmenoglu O, Aydin S. Effects of trapidil on intestinal mucosal barrier function and bacterial translocation after intestinal ischemia and reperfusion in an experimental rat model. Curr Ther Res Clin Exp. 2003;64(6):355–66. https://doi.org/10.1016/s0011-393x(03)00091-2.

62. Colak T, Polat A, Bagdatoglu O, Kanik A, Turkmenoglu O, Aydin S. Effect of trapidil in ischemia/reperfusion injury on rat small intestine. J Investig Surg. 2003;16(3):167–76.
63. Ben Shahar Y, Sukhotnik I, Bitterman N, Pollak Y, Bejar J, Chepurov D, et al. Effect of N-acetylserotonin on intestinal recovery following intestinal ischemia-reperfusion injury in a rat. Eur J Pediatr Surg. 2016;26(1):47–53. https://doi.org/10.1055/s-0035-1559886.
64. Tas U, Ayan M, Sogut E, Kuloglu T, Uysal M, Tanriverdi HI, et al. Protective effects of thymoquinone and melatonin on intestinal ischemia-reperfusion injury. Saudi J Gastroenterol. 2015;21(5):284–9. https://doi.org/10.4103/1319-3767.166203.
65. Yang B, Ni YF, Wang WC, Du HY, Zhang H, Zhang L, et al. Melatonin attenuates intestinal ischemia--reperfusion-induced lung injury in rats by upregulating N-myc downstream-regulated gene 2. J Surg Res. 2015;194(1):273–80. https://doi.org/10.1016/j.jss.2014.11.018.
66. Jiang LL, Zhang JJ, Zhang ZZ, He XH, Chen DL, Wang YL. Effect of intraperitoneal resuscitation with different concentrations of sodium pyruvate on intestinal ischemia reperfusion injury in hemorrhagic shock rat. Shock. 2016;45(4):441–9. https://doi.org/10.1097/shk.0000000000000515.
67. Zhang JJ, Zhang ZZ, Ke JJ, He XH, Zhan J, Chen DL, et al. Protection against intestinal injury from hemorrhagic shock by direct peritoneal resuscitation with pyruvate in rats. Shock. 2014;42(5):464–71. https://doi.org/10.1097/shk.0000000000000230.
68. Tassopoulos A, Chalkias A, Papalois A, Iacovidou N, Xanthos T. The effect of antioxidant supplementation on bacterial translocation after intestinal ischemia and reperfusion. Redox Rep. 2017;22(1):1–9. https://doi.org/10.1080/13510002.2016.1229893.
69. Borges SC, da Silva De Souza AC, Beraldi EJ, Schneider LC, Buttow NC. Resveratrol promotes myenteric neuroprotection in the ileum of rats after ischemia-reperfusion injury. Life Sci. 2016;166:54–9. https://doi.org/10.1016/j.lfs.2016.09.016.
70. Huang X, Zhao W, Hu D, Han X, Wang H, Yang J, et al. Resveratrol efficiently improves pulmonary function via stabilizing mast cells in a rat intestinal injury model. Life Sci. 2017;185:30–7. https://doi.org/10.1016/j.lfs.2017.07.018.
71. Xu X, Li D, Gao H, Gao Y, Zhang L, Du Y, et al. Protective effect of the traditional Chinese medicine xuesaitong on intestinal ischemia-reperfusion injury in rats. Int J Clin Exp Med. 2015;8(2):1768–79.
72. Jiang Y, Zhou Z, Meng QT, Sun Q, Su W, Lei S, et al. Ginsenoside Rb1 treatment attenuates pulmonary inflammatory cytokine release and tissue injury following intestinal ischemia reperfusion injury in mice. Oxidative Med Cell Longev. 2015;2015:843721. https://doi.org/10.1155/2015/843721.
73. Zhu J, Wang P, He Q, Zhou J, Luo C. Evidence of an anti-apoptotic effect of qinghuobaiduyin on intestinal mucosa following burn injury. Exp Ther Med. 2013;6(6):1390–6. https://doi.org/10.3892/etm.2013.1314.
74. Mo LQ, Chen Y, Song L, Wu GM, Tang N, Zhang YY, et al. Osthole prevents intestinal ischemia-reperfusion-induced lung injury in a rodent model. J Surg Res. 2014;189(2):285–94. https://doi.org/10.1016/j.jss.2014.03.026.
75. Shen JT, Li YS, Xia ZQ, Wen SH, Yao X, Yang WJ, et al. Remifentanil preconditioning protects the small intestine against ischemia/reperfusion injury via intestinal delta- and mu-opioid receptors. Surgery. 2016;159(2):548–59. https://doi.org/10.1016/j.surg.2015.07.028.
76. Zhang XY, Liu ZM, Wen SH, Li YS, Li Y, Yao X, et al. Dexmedetomidine administration before, but not after, ischemia attenuates intestinal injury induced by intestinal ischemia-reperfusion in rats. Anesthesiology. 2012;116(5):1035–46. https://doi.org/10.1097/ALN.0b013e3182503964.
77. Gan X, Xing D, Su G, Li S, Luo C, Irwin MG, et al. Propofol attenuates small intestinal ischemia reperfusion injury through inhibiting NADPH oxidase mediated mast cell activation. Oxidative Med Cell Longev. 2015;2015:167014. https://doi.org/10.1155/2015/167014.
78. Zhao W, Zhou S, Yao W, Gan X, Su G, Yuan D, Hei Z. Propofol prevents lung injury after intestinal ischemia-reperfusion by inhibiting the interaction between mast cell activation and oxidative stress. Life Sci. 2014;108(2):80–7. https://doi.org/10.1016/j.lfs.2014.05.009.

79. Gan X, Su G, Zhao W, Huang P, Luo G, Hei Z. The mechanism of sevoflurane preconditioning-induced protections against small intestinal ischemia reperfusion injury is independent of mast cell in rats. Mediat Inflamm. 2013;2013:378703. https://doi.org/10.1155/2013/378703.
80. Liu C, Shen Z, Liu Y, Peng J, Miao L, Zeng W, Li Y. Sevoflurane protects against intestinal ischemia-reperfusion injury partly by phosphatidylinositol 3 kinases/Akt pathway in rats. Surgery. 2015;157(5):924–33. https://doi.org/10.1016/j.surg.2014.12.013.
81. Kim M, Park SW, Kim M, D'Agati VD, Lee HT. Isoflurane post-conditioning protects against intestinal ischemia-reperfusion injury and multiorgan dysfunction via transforming growth factor-beta1 generation. Ann Surg. 2012;255(3):492–503. https://doi.org/10.1097/SLA.0b013e3182441767.
82. Harm S, Gabor F, Hartmann J. Low-dose polymyxin: an option for therapy of Gram-negative sepsis. Innate Immun. 2016;22(4):274–83. https://doi.org/10.1177/1753425916639120.
83. Ji YY, Wang ZD, Wang SF, Wang BT, Yang ZA, Zhou XR, et al. Ischemic preconditioning ameliorates intestinal injury induced by ischemia-reperfusion in rats. World J Gastroenterol. 2015;21(26):8081–8. https://doi.org/10.3748/wjg.v21.i26.8081.
84. Liu KX, Li YS, Huang WQ, Chen SQ, Wang ZX, Liu JX, Xia Z. Immediate postconditioning during reperfusion attenuates intestinal injury. Intensive Care Med. 2009;35(5):933–42. https://doi.org/10.1007/s00134-009-1428-1.
85. Wen SH, Ling YH, Li Y, Li C, Liu JX, Li YS, et al. Ischemic postconditioning during reperfusion attenuates oxidative stress and intestinal mucosal apoptosis induced by intestinal ischemia/reperfusion via aldose reductase. Surgery. 2013;153(4):555–64. https://doi.org/10.1016/j.surg.2012.09.017.
86. Rosero O, Onody P, Kovacs T, Molnar D, Fulop A, Lotz G, et al. Postconditioning: "Tollerating" mesenteric ischemia-reperfusion injury? Surgery. 2017;161(4):1004–15. https://doi.org/10.1016/j.surg.2016.09.031.
87. Li C, Li YS, Xu M, Wen SH, Yao X, Wu Y, et al. Limb remote ischemic preconditioning for intestinal and pulmonary protection during elective open infrarenal abdominal aortic aneurysm repair: a randomized controlled trial. Anesthesiology. 2013;118(4):842–52. https://doi.org/10.1097/ALN.0b013e3182850da5.
88. Shen ZY, Zhang J, Song HL, Zheng WP. Bone-marrow mesenchymal stem cells reduce rat intestinal ischemia-reperfusion injury, ZO-1 downregulation and tight junction disruption via a TNF-alpha-regulated mechanism. World J Gastroenterol. 2013;19(23):3583–95. https://doi.org/10.3748/wjg.v19.i23.3583.
89. Jensen AR, Doster DL, Hunsberger EB, Manning MM, Stokes SM, Barwinska D, et al. Human adipose stromal cells increase survival and mesenteric perfusion following intestinal ischemia and reperfusion injury. Shock. 2016;46(1):75–82. https://doi.org/10.1097/shk.0000000000000571.
90. Jensen AR, Manning MM, Khaneki S, Drucker NA, Markel TA. Harvest tissue source does not alter the protective power of stromal cell therapy after intestinal ischemia and reperfusion injury. J Surg Res. 2016;204(2):361–70. https://doi.org/10.1016/j.jss.2016.05.006.
91. Chang CL, Sung PH, Sun CK, Chen CH, Chiang HJ, Huang TH, et al. Protective effect of melatonin-supported adipose-derived mesenchymal stem cells against small bowel ischemia-reperfusion injury in rat. J Pineal Res. 2015;59(2):206–20. https://doi.org/10.1111/jpi.12251.