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Exploring the Pathophysiological Mechanisms of Acute Gastrointestinal Injury in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: An Integrative Review

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Abstract: ***Acute gastrointestinal injury (AGI) complicating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) represents a complex multisystem pathophysiological phenomenon involving systemic inflammation, hypoxemia, microcirculatory dysfunction, and gut microbiota dysbiosis. Inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), along with hypoxia-inducible factor-1 alpha (HIF-1α), serve as key drivers of gastrointestinal dysfunction. Furthermore, microcirculatory disturbances and dysregulated gut-lung axis interactions exacerbate gastrointestinal barrier impairment. This review systematically analyzes the pathophysiological mechanisms of AECOPD complicated by AGI, focusing on inflammation, hypoxia, microcirculatory dysfunction, and gut microbiota imbalance, aiming to provide a theoretical foundation and reference for clinical management.***

Keywords: Chronic Obstructive Pulmonary Disease, Acute Gastrointestinal Injury, Systemic Inflammation**.**

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition characterized by persistent airflow limitation, primarily caused by prolonged exposure to harmful gases and particulates, such as tobacco smoke. Acute exacerbations of COPD (AECOPD) refer to episodes of sudden worsening of symptoms, including increased dyspnea, cough, sputum production, or changes in sputum characteristics, over a short period. These exacerbations not only impair patients' quality of life and increase hospitalization rates and healthcare costs but also significantly elevate the risk of mortality.

Acute gastrointestinal injury (AGI) is a common manifestation of gastrointestinal dysfunction observed in critically ill patients, often presenting with symptoms such as abdominal pain, diarrhea, and dyspepsia. Epidemiological data indicate a high prevalence of AGI among patients with acute exacerbations of COPD (AECOPD). For instance, one study reported that approximately 30% of hospitalized AECOPD patients exhibit varying degrees of gastrointestinal dysfunction. These patients frequently experience symptoms such as abdominal distension, diarrhea, and nausea, which not only exacerbate the severity of their condition but also prolong hospital stays and increase healthcare costs [1]. Moreover, gastrointestinal dysfunction is closely associated with higher mortality rates in AECOPD patients, underscoring a significant clinical correlation between the two conditions [2]. This review aims to explore the pathophysiological mechanisms underlying AGI complicating AECOPD, providing a theoretical foundation and reference for clinical management.

2. Systemic Inflammatory Response

During acute exacerbations of COPD, the levels of inflammatory mediators in the body are markedly elevated. COPD itself is an inflammatory disease, and the inflammatory response becomes more pronounced during exacerbations. Pro-inflammatory factors, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and C-reactive protein (CRP), are significantly increased in the bloodstream. These mediators not only affect the respiratory system but also reach the gastrointestinal tract via the circulatory system, leading to mucosal damage and functional impairment. TNF-α and IL-1β directly injure the gastrointestinal mucosa by inducing apoptosis and increasing cellular permeability. Meanwhile, IL-6 exacerbates gastrointestinal inflammation indirectly by promoting acute-phase responses and recruiting inflammatory cells.

2.1 TNF-α

TNF-α activates the NF-κB signaling pathway through its receptors TNFR1 and TNFR2. This activation involves the phosphorylation and degradation of IκB proteins, which release NF-κB, allowing its translocation into the nucleus to promote the expression of inflammatory genes such as TNF-α, IL-1β, and IL-6 [3]. The activated NF-κB signaling pathway upregulates the expression of multiple inflammatory mediators, leading to increased permeability of gastrointestinal epithelial cells. For instance, TNF-α enhances the expression of myosin light chain kinase (MLCK), resulting in the dysfunction of tight junction proteins and increased intestinal epithelial permeability, thereby triggering intestinal barrier dysfunction. In the gastrointestinal tract, NF-κB activation is a key mechanism of host response to microbial infection and tissue injury. However, persistent NF-κB activation contributes to chronic inflammation, further increasing epithelial permeability and ultimately causing intestinal barrier leakage.

2.2 IL-1β

As a critical pro-inflammatory cytokine, IL-1β plays a central role in regulating inflammatory responses during the pathophysiology of AECOPD. Studies have demonstrated that IL-1β levels are significantly elevated during AECOPD, leading to the recruitment of inflammatory cells and exacerbation of inflammation in lung tissue [4]. Additionally, IL-1β has been shown to enhance NF-κB activity in pulmonary tissue, resulting in a broader systemic inflammatory response that further worsens the condition of AECOPD patients [5]. Research has revealed that IL-1β selectively reduces the levels of occludin, a transmembrane tight junction protein, in Caco-2 monolayers and murine intestinal epithelial cells, without affecting other tight junction proteins. This effect is mediated by the rapid upregulation of miR-200c-3p, a microRNA that binds to occludin mRNA, leading to its degradation or translational suppression, ultimately reducing occludin protein expression and increasing intestinal epithelial permeability [5]. Moreover, IL-1β activates the NF-κB signaling pathway, enhancing myosin light chain kinase (MLCK) gene activity, which further compromises tight junction integrity and increases permeability [6]. The pivotal role of IL-1β in AECOPD and gastrointestinal dysfunction lies in its ability to regulate tight junction proteins and inflammatory gene expression, resulting in heightened intestinal permeability and aggravated inflammatory responses. These findings collectively suggest that IL-1β, through complex molecular mechanisms, increases intestinal epithelial permeability and, in some cases, indirectly induces epithelial cell damage.

2.3 IL-6

IL-6 plays a critical role in the systemic inflammatory response during AECOPD. As a multifunctional cytokine, IL-6 regulates immune responses, inflammatory processes, and acute-phase reactions. During acute exacerbations of chronic obstructive pulmonary disease (AECOPD), serum IL-6 levels are significantly elevated. IL-6 not only serves as a key pro-inflammatory mediator but also positively correlates with disease severity in AECOPD patients.IL-6 exerts its effects through both the classical signaling pathway and the trans-signaling pathway. In the classical pathway, IL-6 binds to membrane-bound IL-6R, forming a complex that associates with gp130, activating the JAK/STAT signaling cascade. In contrast, the trans-signaling pathway involves IL-6 binding to soluble IL-6R (sIL-6R), which then interacts with membrane-bound gp130 to activate the same signaling cascade [7]. During AECOPD, the trans-signaling pathway is believed to be the primary mechanism of IL-6 action, as sIL-6R is abundantly produced under inflammatory conditions, expanding the range of IL-6 activity [8]. By activating these signaling pathways, IL-6 promotes the proliferation, differentiation, and migration of inflammatory cells, thereby intensifying the inflammatory response. Additionally, IL-6 regulates the acute-phase reaction in the liver by stimulating the production of positive acute-phase proteins (e.g., CRP, serum amyloid A, α1-antitrypsin) while suppressing the production of negative acute-phase proteins (e.g., albumin, transferrin, fibronectin) [9]. This amplifies systemic inflammation, further impairing gastrointestinal function. In gastrointestinal diseases, IL-6 plays a pivotal role by increasing the phosphorylation of tight junction proteins, leading to enhanced epithelial cell permeability. This increased permeability compromises the intestinal barrier function, contributing to gastrointestinal dysfunction and associated complications.

2.4 CRP

During AECOPD, elevated CRP levels not only indicate the severity of inflammation but are also closely associated with patient prognosis. High CRP levels predict increased hospitalization rates and mortality. CRP is markedly elevated at sites of inflammation and infection, where it induces a cascade of inflammatory responses, including activation of the complement system, macrophage phagocytosis, apoptosis, and nitric oxide (NO) release. These CRP-mediated effects exacerbate gastrointestinal inflammation, leading to epithelial cell damage and increased permeability, thereby contributing to gastrointestinal dysfunction [10]. In gastrointestinal dysfunction, elevated CRP levels reflect disruption of the intestinal barrier function, resulting in increased intestinal permeability. This allows bacteria and toxins from the gut to translocate into the bloodstream, further amplifying systemic inflammatory responses [11].

3. Hypoxia and Hypoxemia

Hypoxemia is commonly observed in AECOPD patients as a result of impaired pulmonary function and gas exchange abnormalities. Hypoxemia exerts direct detrimental effects on the gastrointestinal mucosa. Under hypoxic conditions, reduced blood flow to the gastrointestinal mucosa leads to tissue ischemia and metabolic disturbances. Additionally, hypoxia stabilizes hypoxia-inducible factor-1 alpha (HIF-1α), which influences cellular energy metabolism and survival.

3.1 Effects of Hypoxia on Cellular Metabolism

Under hypoxic conditions, cells initiate a series of adaptive mechanisms to maintain energy metabolism and survival, with hypoxia-inducible factor-1 alpha (HIF-1α) serving as the central regulator of the hypoxic response. In normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylases (PHDs), marking it for degradation. Hydroxylated HIF-1α is recognized by the Von Hippel-Lindau protein (pVHL) and subsequently degraded via the ubiquitin-proteasome pathway. Under hypoxic conditions, PHD activity is inhibited, leading to HIF-1α stabilization. The stabilized HIF-1α translocates to the nucleus, where it dimerizes with HIF-1β to form an active transcription factor complex, initiating the expression of genes related to hypoxic adaptation, such as vascular endothelial growth factor (VEGF), glycolytic enzymes, and anti-apoptotic proteins [12]. By activating these genes, HIF-1α promotes angiogenesis and glycolysis, enhancing oxygen and nutrient supply to support cell survival in hypoxic environments. For instance, the upregulation of VEGF facilitates angiogenesis, improving tissue oxygenation. However, prolonged hypoxia and excessive HIF-1α activation may lead to cellular dysfunction and apoptosis. For example, overexpression of VEGF can result in aberrant angiogenesis, which may exacerbate tissue hypoxia and damage [13].

3.2 Effects of Hypoxia on Gastrointestinal Mucosa

Hypoxia primarily affects the gastrointestinal mucosa by

reducing blood flow and disrupting cellular metabolism. The gastrointestinal mucosa is a highly metabolically active tissue requiring a sufficient supply of oxygen and nutrients to maintain its barrier function and cellular renewal. Under hypoxic conditions, reduced mucosal blood flow leads to tissue ischemia and hypoxia, triggering metabolic disturbances and a cascade of pathological responses. Firstly, the expression of tight junction proteins, such as occludin, zonula occludens-1 (ZO-1), and claudin, is reduced under hypoxic conditions. This results in widened intercellular spaces, increased intestinal permeability, and a higher likelihood of bacterial and toxin translocation into the bloodstream, leading to systemic inflammatory responses [14]. Secondly, hypoxia induces oxidative stress in the gastrointestinal mucosa, generating excessive reactive oxygen species (ROS). These ROS further damage cellular structures and functions, triggering inflammation and apoptosis. Studies have shown that oxidative stress plays a crucial role in the pathogenesis of intestinal diseases. ROS activate multiple cellular signaling pathways, including nuclear factor-κB (NF-κB) and stress-activated protein kinase (SAPK) pathways. NF-κB, a key regulator of cellular stress and apoptosis, promotes the release of inflammatory cytokines and initiates apoptosis when activated [15].

3.3 Effects of Hypoxia on Immune Responses

Hypoxia not only directly damages the gastrointestinal mucosa but also indirectly exacerbates inflammation by modulating immune cell function. Under hypoxic conditions, immune cells such as macrophages and neutrophils exhibit enhanced activity, producing increased levels of inflammatory mediators and oxidative stress products. For instance, in a hypoxic environment, macrophage activity is significantly heightened, primarily regulated through the hypoxia-inducible factor (HIF) signaling pathway. HIF-1α and HIF-2α are stabilized and accumulate under hypoxic conditions, driving metabolic reprogramming in macrophages, making them more reliant on glycolysis rather than oxidative phosphorylation. This metabolic shift promotes the differentiation of macrophages into the M1 phenotype, which releases higher levels of pro-inflammatory cytokines such as TNF-α and IL-1β[16]. These inflammatory mediators and oxidative stress products not only further damage the gastrointestinal mucosa but also circulate through the bloodstream, affecting systemic organs and tissues. This contributes to systemic inflammation and the development of multi-organ dysfunction.

4. Microcirculatory Dysfunction

Microcirculatory dysfunction is commonly observed in COPD patients, particularly during acute exacerbations. This dysfunction is not restricted to the respiratory system but also affects the gastrointestinal blood supply. During AECOPD, pulmonary inflammation and hypoxemia contribute to systemic endothelial dysfunction, which subsequently leads to microcirculatory disturbances.

4.1 Mechanisms of Microcirculatory Dysfunction

Under normal conditions, the gastrointestinal tract is richly supplied with blood to meet its high metabolic demands. However, during AECOPD, systemic inflammation and hypoxemia-induced endothelial dysfunction reduce gastrointestinal microcirculation. This microcirculatory dysfunction not only leads to ischemia and hypoxia of gastrointestinal tissues but also triggers the generation of reactive oxygen species (ROS), further damaging cells and tissues. Microcirculation refers to the flow of blood through small vessels, such as capillaries, arterioles, and venules, responsible for delivering oxygen and nutrients to tissues while removing metabolic waste. In COPD patients, systemic inflammation and hypoxemia impair endothelial cell function, characterized by increased vascular permeability, abnormal vascular tone, and altered hemorheology. This endothelial dysfunction results in microvascular constriction and occlusion, ultimately disrupting microcirculation.

4.2 Endothelial Dysfunction

Vascular endothelial cells play a crucial role in maintaining vascular function and microcirculation. Under normal conditions, endothelial cells regulate vasodilation and vasoconstriction by releasing various factors, such as nitric oxide (NO) and prostacyclin (PGI2), ensuring smooth and steady blood flow. However, during AECOPD, systemic inflammation and hypoxemia lead to endothelial dysfunction. Under hypoxic conditions, oxidative stress in endothelial cells increases, significantly reducing the bioavailability of NO, further disrupting vascular function. Research indicates that hypoxia affects the expression and activity of endothelial nitric oxide synthase (eNOS), reducing NO synthesis and contributing to endothelial dysfunction. Moreover, under hypoxia and inflammatory conditions, endothelial cells secrete increased levels of vasoconstrictors such as endothelin-1 (ET-1). ET-1, a potent endogenous vasoconstrictor, works in tandem with reduced NO synthesis to cause vasoconstriction, decreased blood flow, and a vicious cycle of tissue hypoxia [17]. This imbalance exacerbates endothelial dysfunction, worsening the condition of AECOPD patients. Endothelial dysfunction also increases vascular permeability, leading to the leakage of plasma components (e.g., albumin, fibrinogen) into the interstitial spaces, causing edema and triggering localized inflammatory responses. Furthermore, endothelial cells express adhesion molecules such as E-selectin, P-selectin, ICAM-1, and VCAM-1, promoting leukocyte (e.g., neutrophils and monocytes) adhesion and transmigration across the vascular wall. The expression of these adhesion molecules is regulated by inflammatory mediators, and endothelial activation during inflammation intensifies leukocyte adhesion and migration, further aggravating localized inflammation [18].

4.3 Ischemia-Reperfusion Injury

Under the context of microcirculatory dysfunction, gastrointestinal tissues are highly susceptible to ischemia-reperfusion (I/R) injury. I/R injury refers to the severe damage that occurs when blood flow is restored to tissues following a period of ischemia. The primary mechanisms of I/R injury include the generation of reactive oxygen species (ROS), calcium overload, and inflammatory responses. During ischemia, cellular metabolism is disrupted, ATP is depleted, and ion pump function in cell membranes is impaired, leading to intracellular calcium accumulation. Upon reperfusion, a

surge of ROS is produced, which reacts with cellular lipids, proteins, and DNA, causing extensive cellular damage. Additionally, I/R injury activates multiple inflammatory signaling pathways, such as the NF-κB and MAPK pathways, further exacerbating inflammation and promoting apoptosis. Studies have shown that I/R injury induces the phosphorylation of I-κB (NF-κB inhibitor protein) and NF-κB p65 via IKKβ, leading to the rapid degradation of I-κB and the activation of the NF-κB signaling pathway. Activated NF-κB increases the expression of inflammatory mediators such as TNF-α and IL-1β, which intensify inflammation. These mediators perpetuate the activation of NF-κB through autocrine and paracrine mechanisms, forming a positive feedback loop that exacerbates tissue damage and apoptosis [19]. The activation of the MAPK pathway also plays a critical role in I/R injury. I/R injury activates MAPK signaling branches, including ERK, JNK, and p38. These kinases phosphorylate their substrates to regulate cellular stress responses. The activated MAPK pathway promotes the expression of pro-apoptotic genes while inhibiting anti-apoptotic genes, thereby inducing apoptosis. Moreover, the MAPK signaling pathway activates other downstream effectors, further amplifying inflammation and cellular damage [19].

4.4 Oxidative Stress and Antioxidant Imbalance

Oxidative stress refers to the imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense system, leading to cellular and tissue damage. During AECOPD, hypoxemia and inflammatory responses increase ROS production while suppressing the activity of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT). This imbalance results in lipid peroxidation of cell membranes, protein denaturation, and DNA damage. ROS not only directly damage cellular structures but also activate various signaling pathways, such as NF-κB and AP-1, which promote the expression of inflammatory cytokines [20]. Furthermore, ROS oxidize phospholipids and proteins on cell membranes, increasing membrane permeability and allowing calcium ions and other harmful substances to enter cells. This process further exacerbates cellular injury and induces apoptosis [21].

5. Gut Microbiota Dysbiosis

The gut microbiota represents a complex ecosystem, comprising approximately 40 trillion microorganisms in the human gut. To date, around 1,000 distinct bacterial species have been identified, with 30 to 40 being commonly observed. The genetic material of the gut microbiota exceeds that of the human host by more than 150-fold, earning it the designation of the "second genome" of the human body [22]. The gut microenvironment primarily supports the growth of six bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia, and Fusobacteria. At the genus level, Bifidobacterium, Bacteroides, Blautia, and Faecalibacterium are among the most abundant taxa [23]. In patients with acute exacerbations of COPD (AECOPD), the predominant bacterial phylum is Firmicutes, followed by Bacteroidetes, Proteobacteria, Actinobacteria, and Verrucomicrobia. At the family level, Bifidobacteriaceae, Eubacteriaceae, Lactobacillaceae, Micrococcaceae, Streptococcaceae, and Veillonellaceae are more abundant in COPD patients. In contrast, families such as Desulfovibrionaceae, Gastranaerophilaceae, and Selenomonadaceae show reduced abundance. Furthermore, the composition of the gut microbial community varies significantly between individuals [24].

5.1 Functions of Normal Gut Microbiota

Normal gut microbiota plays a crucial role in maintaining human health, consisting of beneficial bacteria (e.g., Lactobacillus and Bifidobacterium) and opportunistic pathogens (e.g., Escherichia coli and Clostridium difficile). Beneficial bacteria support gastrointestinal health through various mechanisms, such as fermenting dietary fiber to produce short-chain fatty acids (SCFAs), inhibiting the growth of harmful bacteria, promoting mucosal immune responses, and preserving intestinal barrier function [25]. SCFAs, including acetate, propionate, and butyrate, are metabolic products of dietary fiber fermentation by gut microbiota and are essential for maintaining gut health. SCFAs contribute to intestinal barrier integrity by serving as an energy source for intestinal epithelial cells, regulating immune responses, and promoting mucus secretion. Additionally, SCFAs exhibit anti-inflammatory effects by inhibiting the NF-κB signaling pathway and reducing the production of inflammatory cytokines [26].

5.2 Causes of Gut Microbiota Dysbiosis

The causes of gut microbiota dysbiosis in AECOPD patients are multifaceted, including prolonged use of antibiotics, corticosteroids, and other medications, an imbalanced diet, and the impact of the chronic disease itself. The extensive use of antibiotics can kill beneficial bacterial populations, leading to the overgrowth of harmful bacteria, such as Clostridium difficile. While corticosteroids are effective in controlling inflammation, long-term use suppresses the immune system and disrupts the balance of gut microbiota. An imbalanced diet is another critical factor contributing to gut microbiota dysbiosis. Due to respiratory difficulty and loss of appetite, AECOPD patients often consume insufficient dietary fiber and essential nutrients, resulting in reduced gut microbiota diversity. Moreover, the systemic inflammatory response associated with chronic disease also affects the composition and function of the gut microbiota.

5.3 Mechanisms of the Gut-Lung Axis

The gut-lung axis refers to the bidirectional regulatory mechanism between gut microbiota and lung health. During acute exacerbations of COPD (AECOPD), gut microbiota dysbiosis impacts lung health through several pathways. Firstly, gut microbiota dysbiosis enhances systemic inflammation, with inflammatory mediators such as IL-6, TNF-α, and IL-1β circulating to the lungs and exacerbating pulmonary inflammation [27]. Secondly, normal gut microbiota produces short-chain fatty acids (SCFAs), which have anti-inflammatory properties. SCFAs modulate immune cell functions, including those of dendritic cells and T cells, to reduce lung inflammation. However, during dysbiosis, the production of SCFAs decreases, thereby worsening pulmonary inflammation. Additionally, dendritic cells and T

cells in the gut, influenced by microbial metabolites, travel to the lungs via the bloodstream and participate in local immune responses. Gut microbiota dysbiosis disrupts these immune cells' functions, particularly by reducing regulatory T cells (Tregs), which results in immune imbalance and exacerbates lung inflammation [28]. Finally, impaired gut barrier function allows bacteria and their toxins to translocate into the bloodstream, triggering systemic immune responses and inflammation. This further exacerbates pulmonary infections and inflammation [27].

6. Conclusion and Future Perspectives

Acute gastrointestinal injury (AGI) complicating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is a complex pathological phenomenon frequently encountered in clinical practice. Its underlying mechanisms involve systemic inflammation, hypoxemia, microcirculatory dysfunction, and gut microbiota dysbiosis. These interconnected mechanisms exacerbate gastrointestinal barrier dysfunction and inflammatory responses, further worsening the patient's condition and prognosis. Current evidence highlights the critical roles of inflammatory mediators, such as TNF-α and IL-6, as well as hypoxia-inducible factor-1 alpha (HIF-1α), in this process. Moreover, microcirculatory disturbances and gut microbiota dysbiosis significantly contribute to gastrointestinal dysfunction. However, the precise molecular mechanisms remain inadequately understood, and the efficacy of existing treatment strategies requires further validation. This review systematically elucidates the pathophysiological mechanisms underlying AGI in AECOPD, providing a theoretical foundation for optimizing diagnostic and therapeutic approaches in clinical practice.

Future research should focus on elucidating the specific mechanisms underlying AGI in AECOPD, particularly the bidirectional regulation between inflammatory signaling pathways and the gut-lung axis. Guided by the principles of precision medicine, individualized therapeutic strategies should be explored, including interventions with probiotics and targeted anti-inflammatory agents. Additionally, the development of early diagnostic and prognostic biomarkers, as well as studies on combined therapies involving antioxidants and gut barrier protectants, represent promising directions. Multidisciplinary research and the development of innovative treatment strategies are expected to enhance the management and quality of life for patients with AECOPD complicated by AGI. These advancements could provide new perspectives for addressing this complex clinical condition.

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