Perioperative Pathophysiology

Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Wu Junyan

Junyan Wu

Sun Yat-Sen Memorial Hospital,
Sun Yat-Sen University

➢ Academic and Administrative Positions

- Second-Class Chief Pharmacist，Director of the Department of Pharmacy，Director of Phase I Clinical Research Center
- Vice President of Guangdong Pharmaceutical Association
- Chairman of Hospital Pharmacy Professional Committee, Guangdong Pharmaceutical Association
- Director of Drug Clinical Comprehensive Evaluation Center, Guangdong Provincial Health Commission
- Vice Chairman of Clinical Pharmacy Professional Committee, China Medical Education Association
- Vice Chairman of Pharmaceutical Information Expert Committee, Institute of Hospital Administration, National Health Commission

➢ Academic Achievements

- Initiated and compiled the Off-label Drug Use Directory of Guangdong Pharmaceutical Association in 2015, which has been updated to the 10th edition to date. Led the formulation of the domestic group standard Evidence-based Evaluation Specification for Off-label Drug Use (T/GDPA 1-2021).
- Served as the chief editor of the monograph Surgical Pharmacy, published by China Medical Science and Technology Press.
- Has published more than 50 papers as the first author and corresponding author in domestic core journals and SCI journals, with one paper published in Lancet Diabetes & Endocrinology.
- Serves as an editorial board member for the Chinese version of AOP Yearbook of Pharmacotherapy and the CPT Clinical Pharmacology and Therapeutics.
- Awarded the IBM Micromedex® Outstanding Contribution Award.

Neuroendocrine Response

(I) Response of the Locus Coeruleus–Sympathetic–Adrenal Medullary System

Central effects

Triggered by the release of norepinephrine in brain regions

Peripheral effects

a rapid rise in plasma catecholamine concentrations

Compensatory significance

① Cardiovascular system: affects cardiac function, causing tachycardia and increased myocardial contractility. It also adjusts peripheral resistance and vascular capacitance, increasing cardiac output and raising blood pressure.
② Respiratory system: bronchodilation and increased alveolar ventilation to meet oxygen demand.
③ Substance and energy metabolism: elevated blood glucose to ensure tissue energy supply.

Adverse effects

① Visceral organ ischemia, with gastrointestinal mucosal erosion, ulceration, and bleeding; ② hypertension;
③ myocardial ischemia; ④ increased leukocyte count and fibrinogen concentration, promoting thrombosis;
⑤ excessive energy consumption, tissue catabolism, and intense vasospasm, leading to severe ischemia of organs and tissues and resulting in functional impairment.

Clarifying the diagnostic criteria for perioperative hypertension: based on changes from baseline blood pressure and threshold values

01

Definition of perioperative hypertension

The diagnosis of perioperative hypertension should integrate both changes from baseline blood pressure and absolute values. An increase in blood pressure of more than 30% over baseline, or reaching SBP ≥140 mmHg and/or DBP ≥90 mmHg, can be defined as perioperative hypertension, improving the accuracy of identification.

02

Definition of hypertensive crisis

Perioperative hypertensive crisis refers to a rapid, marked rise in blood pressure within a short period to above 180/110 mmHg. This state can readily trigger cardiovascular and cerebrovascular events and requires urgent intervention to prevent progression of target-organ damage.

03

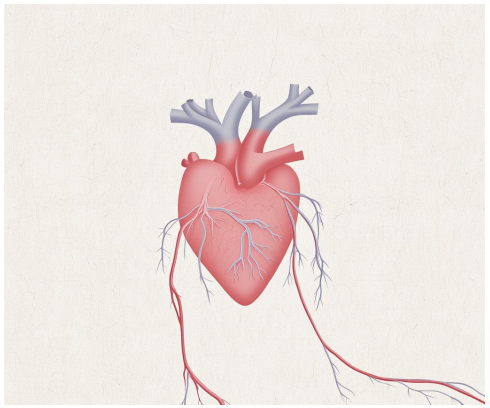
Dynamic monitoring

Twenty-four-hour ambulatory blood pressure monitoring can be performed to help distinguish white-coat hypertension from masked hypertension. It enables precise assessment of true blood pressure levels and provides a basis for individualized management.

Perioperative heart rate levels significantly affect the incidence of adverse cardiac events

Risk comparison

In patients with a perioperative **heart rate >100** beats/min, the incidence of adverse cardiac events is as high as 23.4%, significantly higher than the 7.1% observed in those with a heart rate <60 beats/min, indicating that heart rate control is crucial.



Mechanistic explanation

An excessively fast heart rate increases myocardial oxygen consumption; in particular, patients with coronary artery stenosis are prone to myocardial ischemia, which can in turn lead to serious complications such as angina and myocardial infarction.

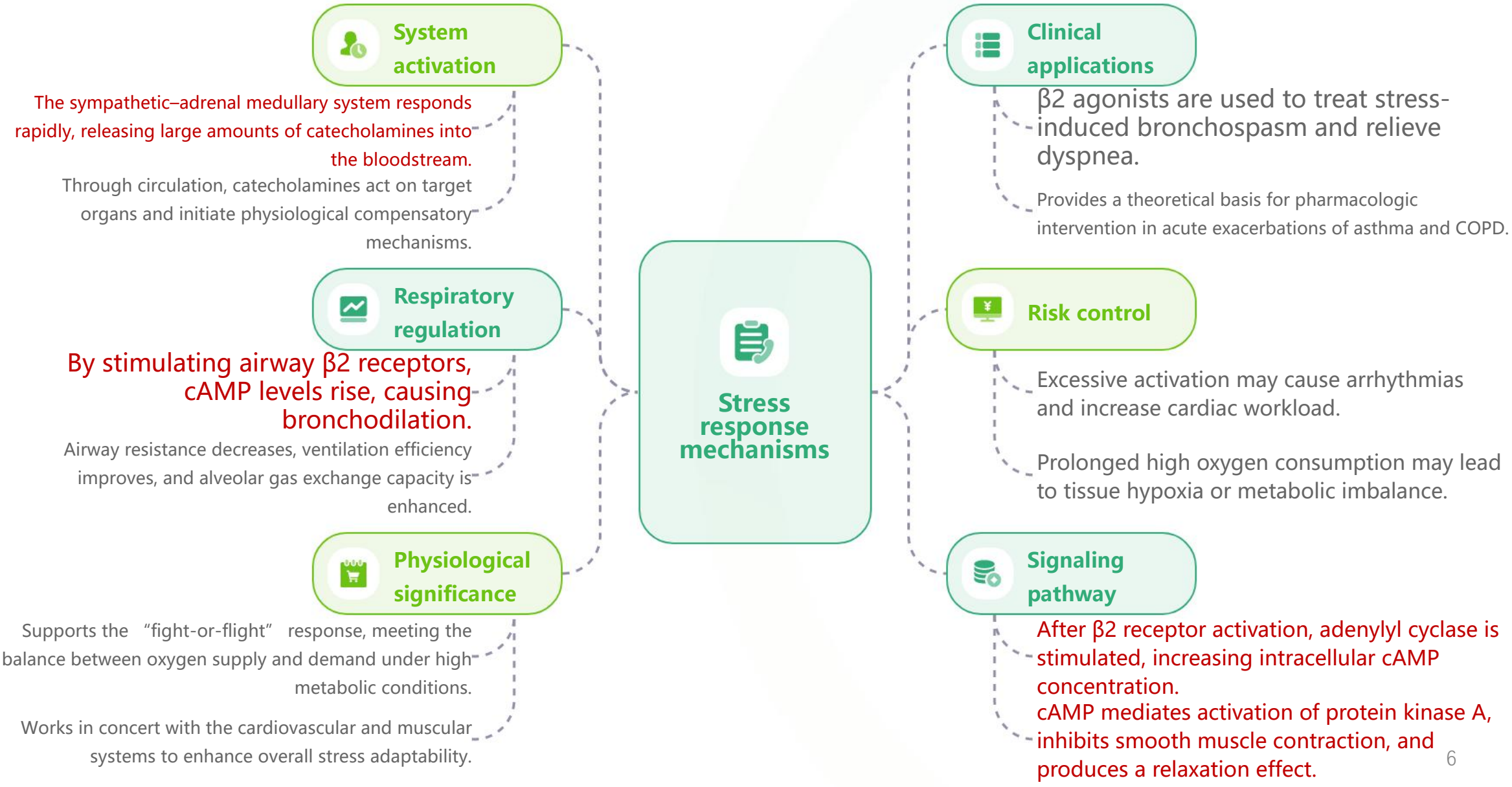
Clinical impact

Tachycardia can cause hemodynamic instability, increase the risk of intraoperative arrhythmias and postoperative heart failure, and adversely affect anesthetic safety and surgical prognosis.

Management implications

Early identification of patients with elevated heart rates and timely intervention can help reduce the risk of perioperative cardiovascular events and improve surgical safety and the quality of recovery.

Respiratory system



In the resting state, airway clearance capacity decreases, making sputum retention and hypoxemia more likely.

01
Impaired clearance mechanisms

Postoperative patients are less active; breathing becomes shallow and ciliary movement weakens, leading to reduced airway self-clearing capacity.

02
Difficulty expectorating sputum

Incisional pain and analgesics suppress the cough reflex, making it difficult to cough up secretions effectively.

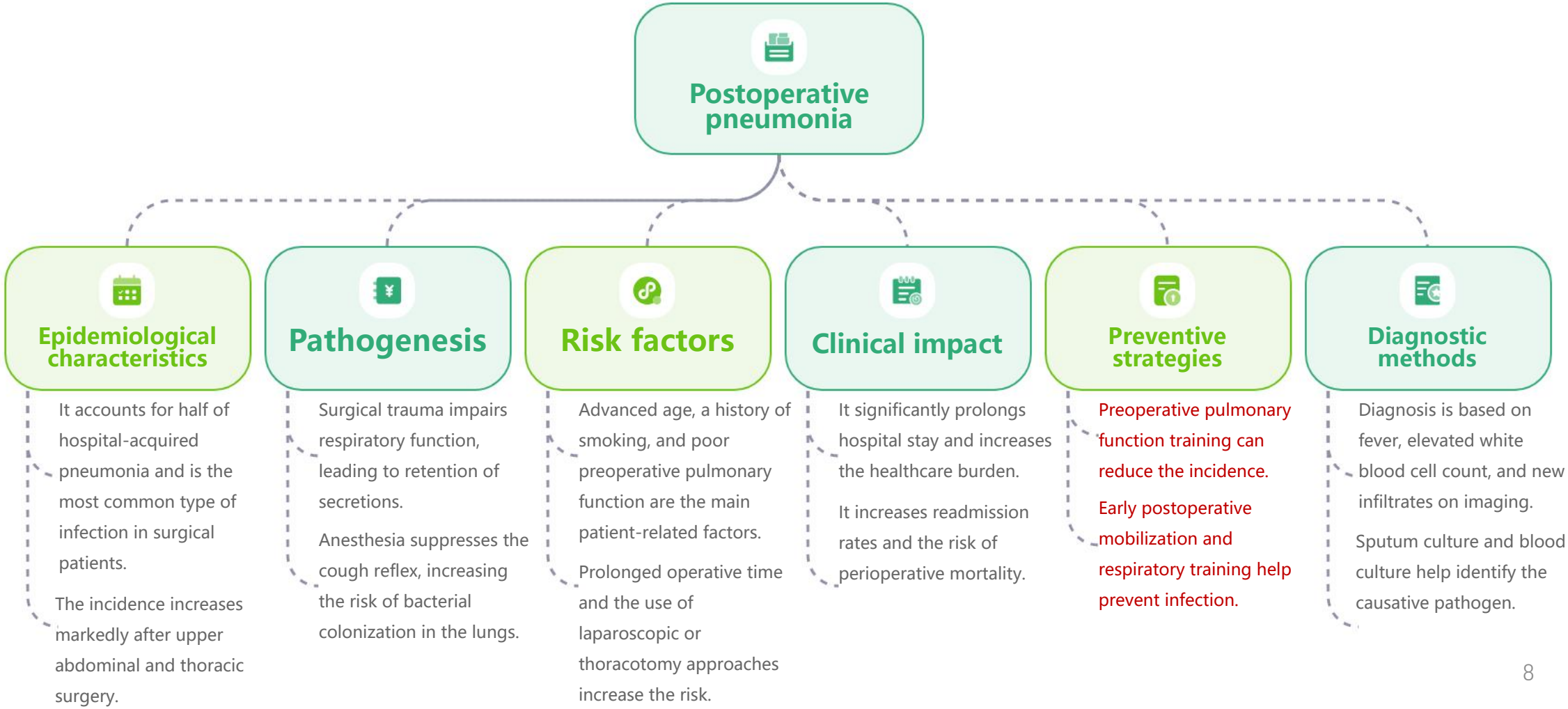
03
Risk of secretion accumulation

Sputum retained in the airway forms localized obstruction, increasing the risk of infection and atelectasis.

04
Triggers of hypoxemia

Airway obstruction causes inadequate ventilation, resulting in impaired oxygenation and worsening postoperative respiratory insufficiency.

Postoperative pneumonia accounts for 50% of hospital-acquired pneumonia and is a major infectious complication in surgical patients.



Age ≥75 years, long-term smoking history, and chronic lung diseases such as COPD are independent risk factors.

Risk associated with advanced age

In patients aged ≥75 years, respiratory function declines and airway defense mechanisms weaken, increasing the risk of postoperative complications.

Effects of smoking

Long-term smoking causes airway inflammation and increased secretions, raising the risk of postoperative sputum retention and pulmonary infection.

COPD comorbidity

In patients with concomitant COPD, reduced pulmonary reserve and ventilatory impairment are independent predictors of postoperative pulmonary complications.

Perioperative safety

Advanced age, smoking, and COPD together significantly affect perioperative respiratory safety and require comprehensive assessment and management.

Activation of the sympathetic–adrenal medullary system triggers gastrointestinal mucosal ischemia, forming the core pathogenic basis of stress ulcers.

Disrupted energy metabolism

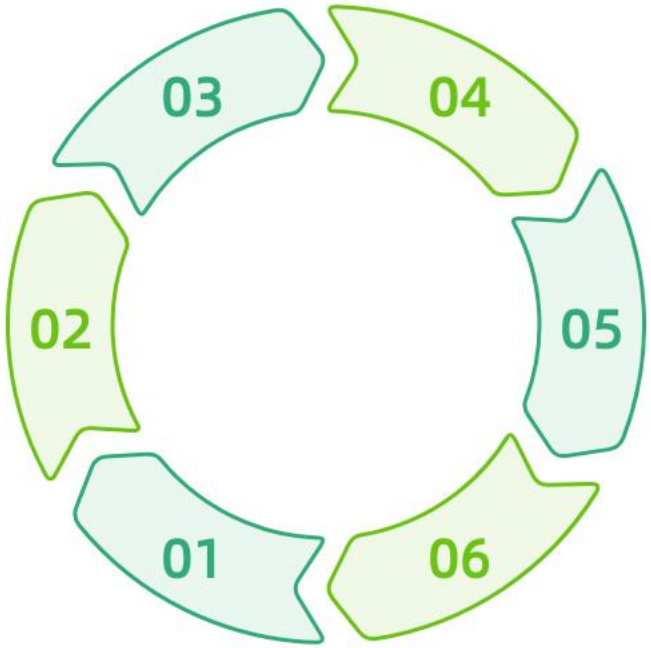
Energy metabolism in mucosal epithelial cells is impaired, repair capacity declines, and the tissue struggles to cope with ongoing injurious stimuli.

Vasoconstriction and ischemia

Catecholamines cause constriction of small splanchnic vessels, reducing blood flow to the gastrointestinal mucosa and resulting in mucosal ischemia and hypoxia, which impairs barrier function.

Activation of the stress system

Under stress, the sympathetic–adrenal medullary system is strongly activated, leading to massive catecholamine release and a series of physiological responses.



Worsened acid–enzyme erosion

Gastric acid and proteases continue to act on the damaged mucosa, accelerating tissue destruction and promoting the formation of erosions or ulcers.

Weakened protective function

Stress inhibits prostaglandin synthesis, reduces mucus secretion and blood flow, and weakens the stomach’ s intrinsic mucosal defense mechanisms.

Clinical manifestations of ulcers

Stress ulcers are mostly acute, multiple, superficial lesions; they are often painless but can cause gastrointestinal bleeding, presenting as hematemesis or melena.

Acute stress triggers a hypercoagulable state: platelet activation, increased coagulation factors, and the dual effects of enhanced fibrinolysis

Hypercoagulable state

Acute stress activates the sympathetic–adrenal system, promoting platelet activation and aggregation while increasing the concentrations of multiple coagulation factors, thereby placing the blood in a hypercoagulable state. This change facilitates rapid hemostasis but also increases the risk of thrombosis.

Platelet activation

Catecholamines enhance platelet reactivity via β-adrenergic receptors, promoting adhesion and aggregation. This can accelerate coagulation during tissue injury, but it may also trigger microvascular occlusion.

Enhanced fibrinolysis

In the early phase of stress, the fibrinolytic system is activated in parallel to prevent excessive thrombus formation and maintain coagulation balance. However, this compensatory mechanism is short-lived; persistent stress leads to exhaustion of fibrinolytic function.

Dual effects

The coexistence of hypercoagulability and fibrinolysis constitutes a dual defensive mechanism in acute stress, ensuring hemostasis while preventing thrombus propagation. When this balance is disrupted, severe complications such as disseminated intravascular coagulation can be readily precipitated.

Leukocytosis and bone marrow hyperplasia: stress-induced immune mobilization with both anti-infective benefits and pro-inflammatory risks

Acute immune mobilization

Stress activates the sympathetic nervous system, prompting the bone marrow to release large numbers of neutrophils and raising the peripheral white blood cell count. A left shift indicates that immature cells have entered the bloodstream, enhancing the body’ s ability to fight infection.

Increased pro-inflammatory risk

Dysregulated catecholamine and glucocorticoid signaling can induce the release of pro-inflammatory cytokines such as IL-6 and TNF-α. Persistent stress can drive inflammation out of control, increasing the risk of tissue damage and chronic disease.

Compensatory bone marrow hyperplasia

Stress signals stimulate hematopoietic stem cell proliferation via β-adrenergic receptors, increasing granulopoiesis. This is an adaptive response, but over the long term it may lead to excessive depletion of bone marrow reserves.

Immune dysfunction

After an initial boost in immunity, if stress persists, T-cell activity is suppressed and antibody production decreases. This manifests as reduced resistance to infection and a greater susceptibility to autoimmune or chronic inflammatory diseases.

Neuroendocrine responses

(II) Responses of the hypothalamic–pituitary–adrenal cortex (HPA) axis

Central effects

Central effects of HPA-axis activation

Peripheral effects

A rapid and marked rise in plasma glucocorticoid (GC) concentration

Compensatory significance

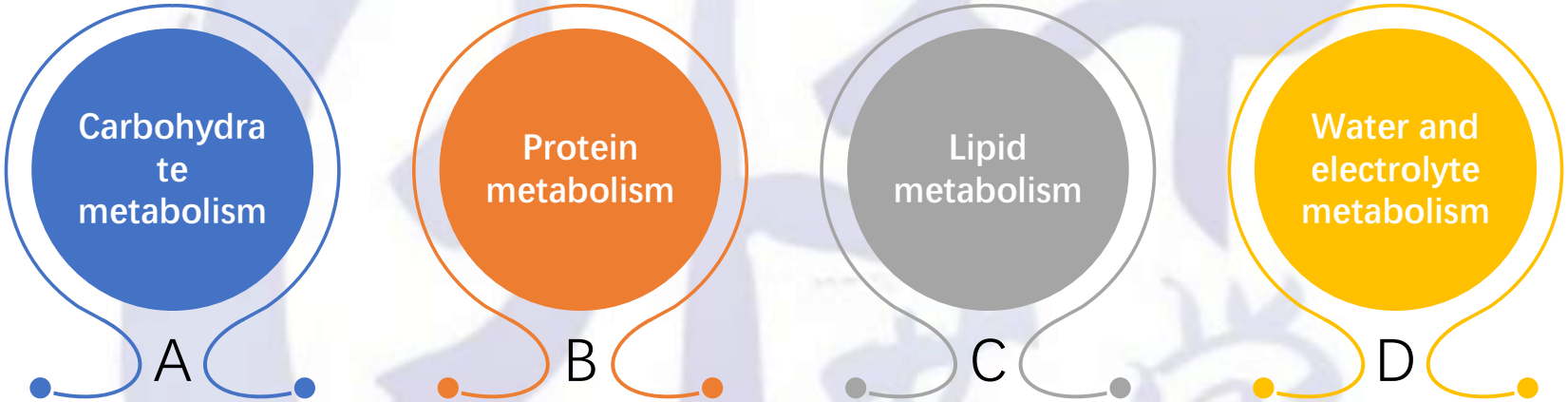
Glucocorticoids secreted by the adrenal cortex are key mediators of the stress response; during the perioperative period, critically ill patients may develop relative adrenal insufficiency.

① Metabolic effects: increased blood glucose; ② Permissive effects of glucocorticoids: they enable other hormones to act—glucocorticoids ensure the lipolytic (fat-mobilizing) actions of catecholamines and glucagon; responsiveness to catecholamines plays an important role in maintaining blood pressure; ③ Stabilize cell membranes and lysosomal membranes, reducing cellular injury; they can inhibit the production of multiple inflammatory mediators and cytokines; ④ Powerful anti-inflammatory effects.

Adverse effects

① Marked suppression of immune responses; ② Growth and developmental retardation and poor wound healing; ③ Suppression of the gonadal axis.
④ Suppression of the thyroid axis; ⑤ Abnormal metabolism, manifested as hyperlipidemia, hyperglycemia, etc.

Physiological actions of glucocorticoids



Physiological doses of adrenal glucocorticoids are essential for life and can affect the metabolism of carbohydrates, proteins, lipids, water, electrolytes, and other substances, as well as the functions of multiple tissues and organs.

Physiological Effects of Glucocorticoids

- **Carbohydrate metabolism—one of the key hormones regulating carbohydrate metabolism in the body**

Mechanisms for raising blood glucose:

Inhibit glucose utilization by peripheral tissues

Increase hepatic gluconeogenesis and provide substrates required for gluconeogenesis

Slow down the oxidative breakdown of glucose

Mechanisms for increasing glycogen content:

Promote hepatic glycogen synthesis, increasing liver glycogen and muscle glycogen stores

Excess adrenal glucocorticoids can cause steroid-induced diabetes mellitus, whereas deficiency can lead to hypoglycemic reactions

As the body’ s primary energy source, carbohydrates supply 50%–70% of energy needs under normal physiological conditions.

Perioperative metabolism

Under stress states such as the perioperative period, the body’ s energy demand increases markedly. Carbohydrate metabolism accelerates to meet high energy consumption. At this time, the capacity to regulate blood glucose affects recovery speed and the risk of complications.

Catabolism

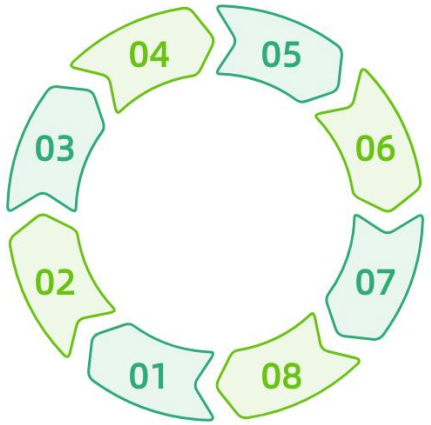
Carbohydrates are broken down through pathways such as glycolysis and the tricarboxylic acid (TCA) cycle, releasing ATP for cellular use. These metabolic processes are precisely regulated by hormones and enzymes, ensuring a dynamic balance between energy supply and energy expenditure.

Energy-providing substances

Carbohydrates are key energy-providing substances that make up living organisms, supplying the main energy required for life activities. In a healthy person, 50%–70% of energy comes from the catabolism of carbohydrates. Their efficient energy-yielding properties give them a central role in physiological activities.

Definition of carbohydrates

Carbohydrates are polyhydroxy aldehydes or ketones and their derivatives; chemically, they are also known as carbohydrates. They are composed of carbon, hydrogen, and oxygen and have specific functional-group structures. They are among the important organic compounds in living organisms.



Homeostasis of the internal environment

Stable carbohydrate metabolism helps maintain balanced blood glucose levels and energy supply. It is crucial for preventing metabolic disturbances such as hypoglycemia or hyperglycemia and is one of the fundamental safeguards enabling the body to cope with stress.

Structural components of organisms

Beyond providing energy, carbohydrates participate in building cellular structures, such as the formation of glycoproteins and glycolipids. They play important roles in cell recognition and signal transduction and are integral to the complex functions of living systems.

Stress response

Under stress, epinephrine and cortisol promote glycogenolysis and gluconeogenesis, increasing blood glucose concentrations to support the function of vital organs. This highlights the key role of carbohydrate metabolism in emergency response mechanisms.

Metabolic regulation

Insulin and glucagon jointly regulate carbohydrate synthesis and breakdown, keeping blood glucose fluctuations within the normal range. Dysregulation may lead to metabolic diseases such as diabetes.

Surgery and anesthesia, as stressors, can markedly affect glucose metabolism, leading to elevated blood glucose and triggering stress hyperglycemia.

01

Stress hyperglycemia

Surgical trauma activates the stress response, promoting glycogenolysis and gluconeogenesis, thereby raising blood glucose.

02

Neuroendocrine regulation

Increased release of hormones such as catecholamines and cortisol inhibits insulin action and exacerbates hyperglycemia.

03

Risk in patients with diabetes

Individuals with preoperative abnormalities in glucose metabolism are more prone to marked fluctuations in blood glucose, making management more difficult.

04

Significant clinical impact

Hyperglycemia is closely associated with postoperative infection, delayed wound healing, and increased mortality.

Lipids are an important form of energy storage in the body, with triglycerides serving as the principal energy-storage molecules.

Definition of lipids

Lipids are compounds that are insoluble in water but soluble in organic solvents. They mainly include two major categories: fats and lipoids. They have important physiological functions in living organisms.

Main classifications

Lipids are mainly divided into fats and lipoids. Fats are predominantly triglycerides. Lipoids include phospholipids, cholesterol, and others.

Triglyceride structure

They are formed by the combination of one glycerol molecule with three fatty acid molecules. This is the most common storage form among lipids and is found mainly in adipose tissue.

Form of energy storage

Triglycerides are the body’ s primary energy reserve. They can be broken down to supply energy during starvation or stress. Per gram, fat releases more energy than proteins and carbohydrates.

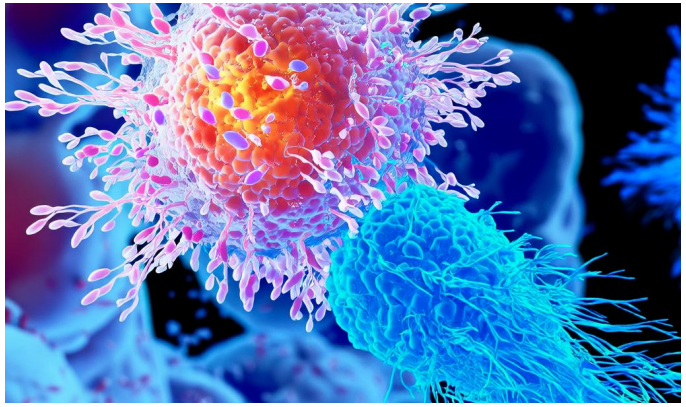
Breakdown and energy-yielding process

Under hormonal regulation, triglycerides can be hydrolyzed into glycerol and fatty acids. Fatty acids generate energy through β-oxidation, providing the body with large amounts of ATP.

Physiological significance

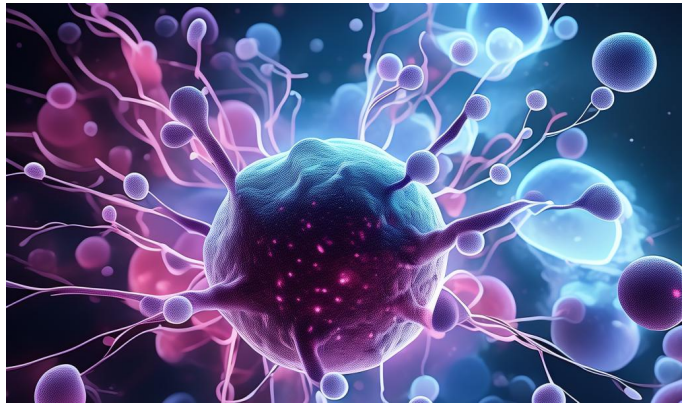
They help maintain energy balance and metabolic stability, protect internal organs and aid in heat insulation, and participate in cell signaling and the construction of membrane structures.

Surgical stress activates hormone-sensitive lipase via catecholamines and inflammatory mediators, promoting lipolysis and fat mobilization.



Stress-hormone–driven

Surgical trauma activates the sympathetic nervous system, triggering catecholamine release and strongly stimulating hormone-sensitive lipase activity in adipose tissue.



Synergy of inflammatory mediators

Cytokines such as TNF-α and IL-1 enhance lipase action, accelerating the release of fatty acids from triglycerides into the bloodstream.

Rapid energy mobilization

Extensive breakdown of adipose tissue provides free fatty acids as an important alternative energy source under stress.

In severe illness, lipoprotein lipase is inhibited, leading to impaired triglyceride clearance and tissue accumulation.

Suppressed enzyme activity

In severe sepsis, endotoxin and TNF-α inhibit lipoprotein lipase activity, reducing triglyceride hydrolysis.

Reduced clearance capacity

Impaired lipoprotein lipase function hinders plasma triglyceride clearance, causing hypertriglyceridemia.

Tissue lipid accumulation

Unoxidized fatty acids deposit in peripheral tissues such as the heart, liver, and pancreas, resulting in lipotoxic injury.

Triglyceride deposition in peripheral tissues induces lipotoxicity, impairing cardiac, hepatic, and pancreatic function.

Mechanisms of lipotoxicity

Incomplete fatty acid oxidation leads to triglyceride deposition in non-adipose tissues, causing cellular dysfunction and apoptosis.

Multi-organ injury

Lipid accumulation in organs such as the myocardium, liver, and pancreas can lead to reduced contractile function and insulin resistance.

Clinical relevance

Lipotoxicity is closely associated with postoperative metabolic disturbances and an increased risk of organ failure, adversely affecting outcomes in critically ill patients.

Perioperative stress increases protein breakdown and decreases protein synthesis, resulting in a negative nitrogen balance.

Suppressed protein synthesis

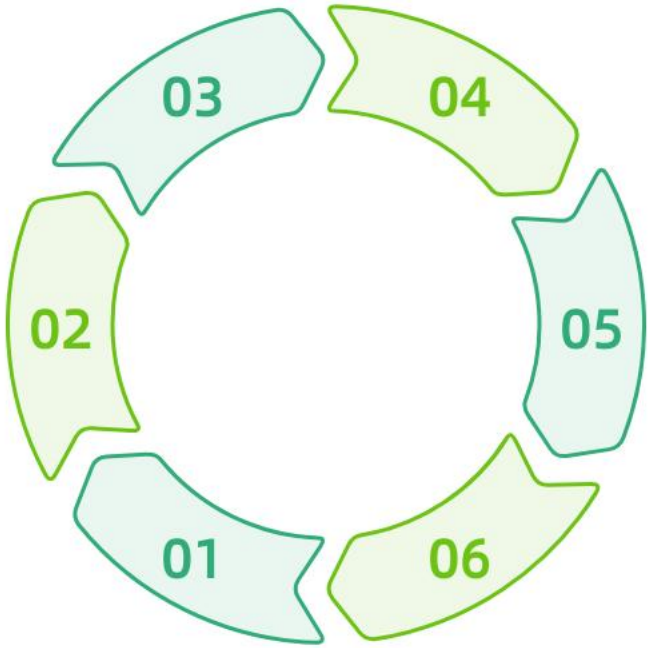
Energy is preferentially supplied to vital organs, and protein-synthesis pathways are inhibited. Insufficient substrates for tissue repair delay wound healing. Reduced synthesis further aggravates metabolic imbalance.

Increased protein breakdown

The inflammatory response markedly increases the rate of protein breakdown, leading to substantial depletion of muscle tissue. The breakdown products are used for emergency energy supply, resulting in impairment of the body’ s structure and function.

Activation of the stress response

Surgical trauma triggers the body’ s stress response, activates inflammatory pathways, and promotes catabolism. This process releases large amounts of inflammatory mediators, exacerbating metabolic disturbances. The stress state continues to affect the course of postoperative recovery.



Development of negative nitrogen balance

Protein breakdown exceeds synthesis, and urinary nitrogen excretion increases significantly. An imbalance between nitrogen intake and output manifests as a negative nitrogen balance, reflecting a state of net protein loss.

Hypermetabolic state

During the perioperative period, the body is in a hypermetabolic, high-consumption state with increased energy demands. Catabolism predominates, increasing the risk of malnutrition and affecting the speed of recovery and prognosis.

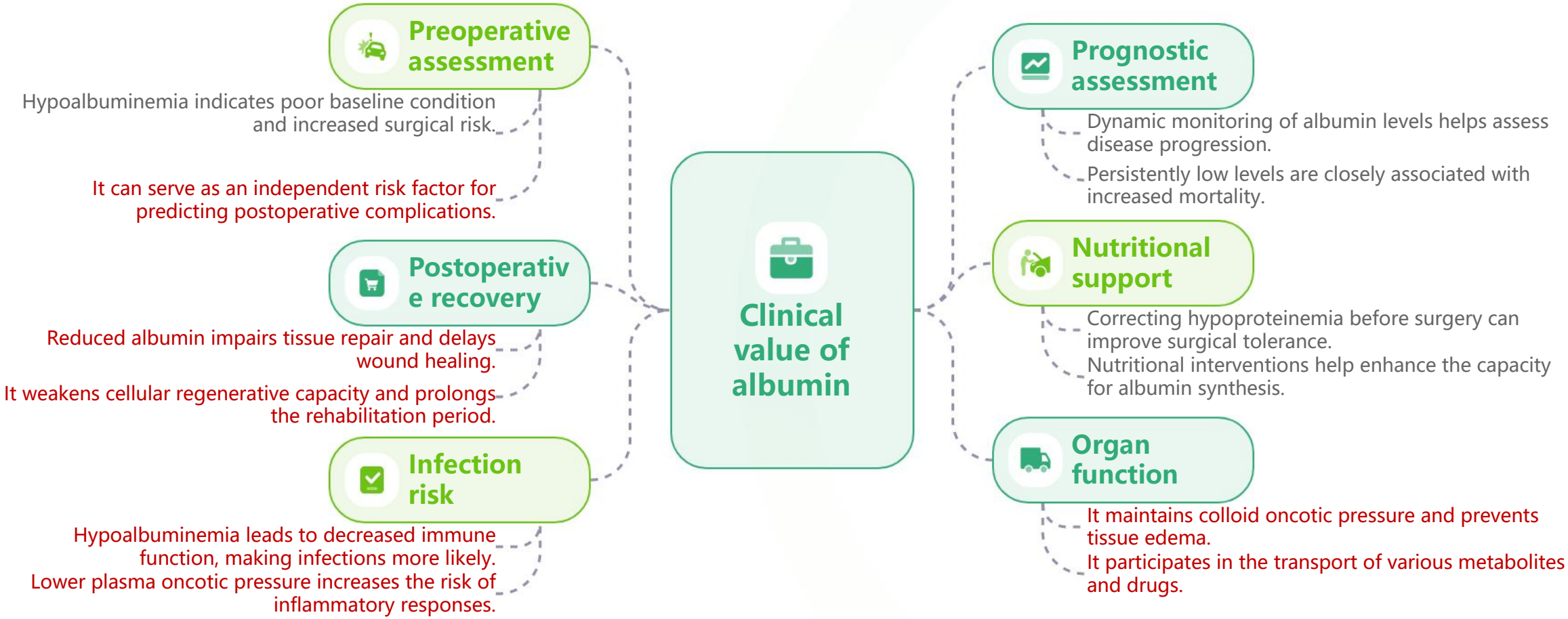
Worsened nutritional depletion

Persistent catabolism rapidly depletes fat and muscle reserves. Inadequate nutritional support will prolong the recovery period. Timely intervention helps improve clinical outcomes.

Effects of increased glucocorticoid secretion on water and electrolytes

1. **At physiological concentrations, it promotes sodium reabsorption and the excretion of potassium, calcium, and phosphate, exerting a weak mineralocorticoid-like effect of sodium retention and potassium excretion.**
2. **When adrenal glucocorticoids are excessive, binding to 11β-hydroxysteroid dehydrogenase becomes saturated; thus, they can bind to mineralocorticoid receptors, promoting sodium–potassium exchange in the distal renal tubules and leading to water and sodium retention and potassium loss.**
3. **Excess adrenal glucocorticoids enhance tissue protein catabolism, causing potassium to be released from within cells.**

Low albumin levels are significantly associated with increased postoperative complications, higher mortality, and delayed healing.



Hypoalbuminemia is regarded as an important biological marker of the malnutrition–inflammation syndrome.

Definition and synthesis

Albumin is synthesized by hepatocytes, accounting for 50%–60% of total plasma protein; it has a half-life of 18–20 days and reflects the liver’ s synthetic function.

Postoperative prevalence

Trauma-related stress, fasting, and preoperative malnutrition lead to negative nitrogen balance, resulting in a high incidence of postoperative hypoalbuminemia.

Association with complications

Low albumin levels delay tissue healing, weaken anti-infective capacity, and significantly increase the risk of postoperative complications and death.

Syndrome marker

Hypoalbuminemia is a key indicator of the malnutrition–inflammation syndrome, suggesting that the body is in a state of severe stress.

Neuroendocrine responses

(III) Other neuroendocrine responses

1 **Increased secretion of β-endorphin**

β-Endorphin binds to opioid receptors to exert an analgesic effect.

2 **Increased glucagon secretion and decreased insulin secretion**

Hyperglycemia has an inhibitory effect on immune responses.

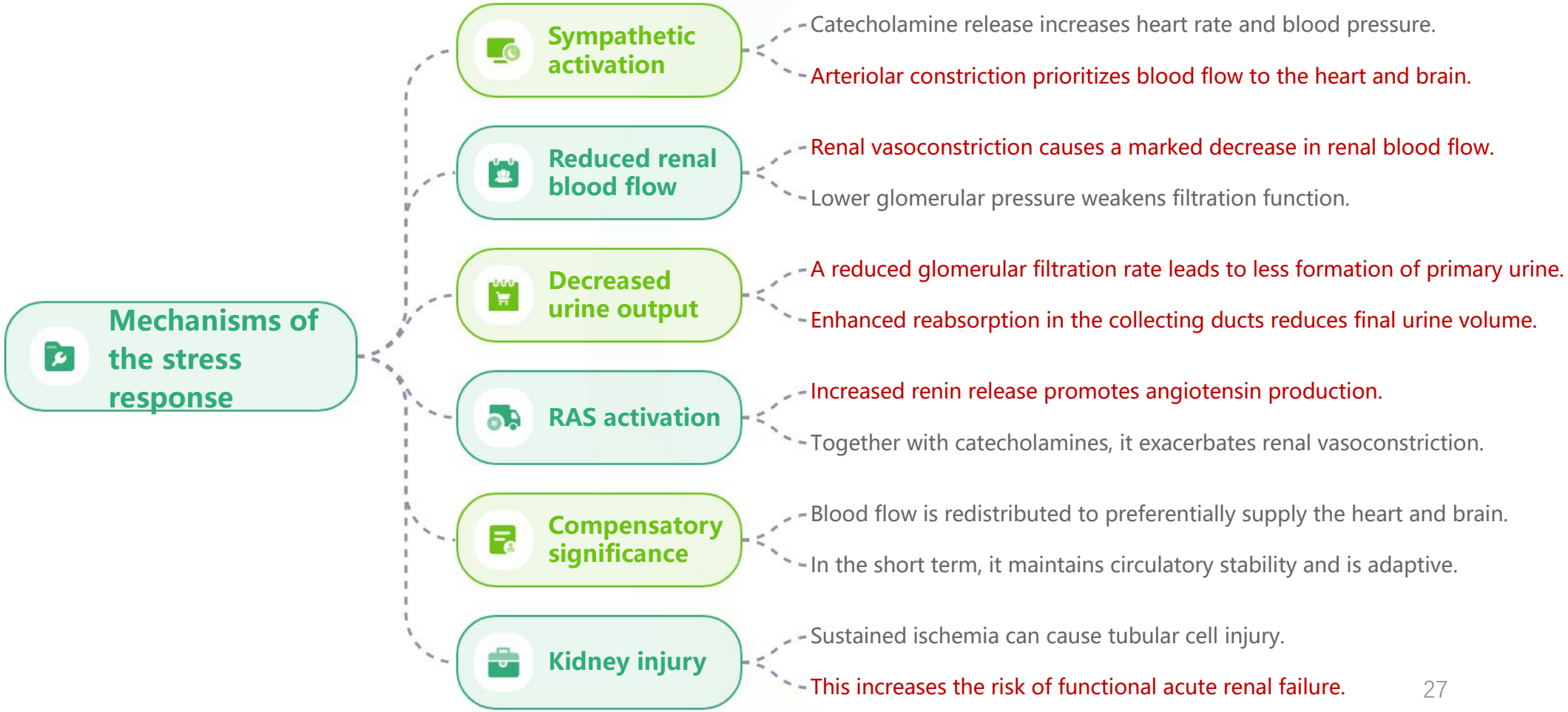
3 **Elevated levels of antidiuretic hormone and aldosterone**

The renin–angiotensin–aldosterone system is activated, leading to increased aldosterone levels. Aldosterone is a mineralocorticoid that can increase renal tubular reabsorption of sodium and water, thereby reducing urine output.

4 **Activation of the parasympathetic nervous system**

Parasympathetic activation triggers intestinal and bladder emptying responses such as diarrhea and urination. During stress, parasympathetic excitation may place the body in a quiescent, withdrawn state, with manifestations including bradycardia, decreased blood pressure, increased gastrointestinal peristalsis, profuse sweating, and syncope.

Stress activates the sympathetic–adrenal medullary system, triggering renal vasoconstriction and a decrease in glomerular filtration rate.



Perioperative pharmacokinetic (PK) changes and clinical medication use

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Suppressed gastrointestinal function

Surgical stress and anesthetic agents slow gastrointestinal peristalsis, impairing the absorption of orally administered drugs.

1	**Delayed gastric emptying**	Surgical stress, anesthetic agents, and opioids used for postoperative pain management can all inhibit gastrointestinal motility, prolonging gastric emptying time.
2	**Slower and less predictable absorption**	Delayed gastric emptying slows the passage of oral drugs into the small intestine, resulting in delayed absorption and a later time to peak concentration; bioavailability also becomes less predictable due to interindividual variability.
3	**Clinical medication considerations**	Before surgery, assess the necessity of oral medications; non-urgent drugs may be withheld. During the postoperative stress period, the dose and frequency of oral administration should be adjusted according to the recovery of gastrointestinal function.

Intestinal perfusion and body temperature

Intestinal hypoperfusion and temperature changes are two other key factors affecting drug absorption.

01

Intestinal hypoperfusion

Intraoperative blood loss, hypotension, or shock can lead to inadequate intestinal perfusion, impairing the absorptive function of intestinal mucosal cells and markedly reducing the amount of drug absorbed.

02

Postoperative ileus

Complications such as ileus and intestinal obstruction, which are common after abdominal surgery or general anesthesia, can further hinder normal drug absorption in the intestine.

03

Impact of temperature changes

Hypothermia can slow local tissue blood flow, affecting the absorption rate of drugs administered subcutaneously or intramuscularly and delaying onset of action.

Blood volume and blood flow

Changes in effective circulating blood volume are the primary factor affecting drug distribution.

1 **Decreased blood volume**

Surgical blood loss, preoperative fasting (no food or fluids), and post-anesthetic vasodilation can all reduce effective circulating blood volume, leading to hemodynamic instability.

2 **Reduced Vd of hydrophilic drugs**

For hydrophilic drugs that are mainly distributed in blood and extracellular fluid—such as neuromuscular blocking agents and some antibiotics—the apparent volume of distribution (Vd) decreases as blood volume decreases.

3 **Abnormally elevated plasma drug concentrations**

A reduced Vd means the drug is “concentrated” within a smaller body-fluid space, resulting in abnormally elevated plasma concentrations; induction-dose anesthetics are more likely to be overdosed, increasing risks such as hypotension.

Plasma protein binding

The acute-phase response triggered by surgical stress alters plasma protein levels, thereby affecting the free (unbound) drug concentration.

1

Decreased albumin levels

Factors such as surgical trauma, inflammatory responses, and hemodilution can reduce serum albumin concentration.

2

Increased α1-acid glycoprotein

As an acute-phase reactant, α1-acid glycoprotein (AAG) is synthesized in increased amounts after surgical stress.

3

Changes in free drug concentration

A decrease in albumin lowers the protein-binding rate of weakly acidic drugs (e.g., barbiturates and benzodiazepines), increasing the free drug concentration, enhancing effects, and even causing toxicity.

4

Increased AAG (α1-acid glycoprotein)

An increase in AAG raises the protein-binding rate of weakly basic drugs (e.g., local anesthetics and opioids), decreasing the free drug concentration and potentially weakening drug effects.

Tissue perfusion and edema

Changes in cardiac output and shifts in body fluids further complicate the drug distribution process.

01

Altered perfusion priorities

In hypovolemia or shock, to ensure blood supply to vital organs such as the heart and brain, the body reduces perfusion to tissues such as muscle and fat.

02

Faster onset of lipophilic drugs

With cerebral perfusion preferentially maintained, lipophilic anesthetics can reach their sites of action more quickly, shortening the time to onset.

03

Prolonged elimination half-life

Reduced perfusion of muscle and adipose tissue slows the clearance of drugs from these tissues, prolonging the elimination half-life.

04

Third-space edema

Surgical trauma and inflammatory responses increase vascular permeability, causing body fluids and hydrophilic drugs to shift into the interstitial space, increasing Vd while correspondingly slowing elimination.

Decreased hepatic blood flow

Anesthesia and surgical stress can markedly affect hepatic blood perfusion.

01

Reduced hepatic perfusion

The vasodilatory effects of anesthetic agents, intraoperative hypotension, and sympathetic activation under stress can all reduce hepatic arterial and portal venous blood flow.

02

Decreased clearance of high-extraction drugs

For drugs with a strong hepatic first-pass effect (high extraction ratio), such as fentanyl, propofol, and lidocaine, systemic clearance is highly dependent on hepatic blood flow; therefore, clearance slows significantly.

Enzyme Activity and Body Temperature

The activity of hepatic drug-metabolizing enzymes is inhibited by multiple perioperative factors.

Effects of Hypothermia

For every 1°C decrease in body temperature, the whole-body metabolic rate decreases by about 7%. Hypothermia directly inhibits the activity of hepatic microsomal enzymes, slowing drug metabolism.

01

Hypoxia and Acidosis

Metabolic disturbances such as hypoxia and acidosis that may occur intraoperatively or postoperatively further suppress hepatic enzyme function and prolong the duration of drug action.

02

Inflammatory Responses Inhibit CYP450

Inflammatory mediators released by surgical trauma and infection (e.g., IL-6) can downregulate the expression and activity of the hepatic cytochrome P450 (CYP450) enzyme system, slowing the metabolism of multiple drugs and increasing the risk of accumulation.

03

Renal Blood Flow and GFR

Decreases in renal blood flow and glomerular filtration rate (GFR) are the core mechanisms underlying delayed postoperative drug excretion.

1

Renal Vasoconstriction

Intraoperative hypotension, dehydration, sympathetic activation, and the use of catecholamine drugs can all cause renal vasoconstriction.

2

Decreased GFR

Reduced renal blood flow directly leads to a decrease in glomerular filtration rate (GFR), affecting drugs excreted unchanged by the kidneys.

3

Delayed Drug Clearance

For drugs primarily eliminated by the kidneys—such as aminoglycosides, vancomycin, and some neuromuscular blocking agents—clearance decreases markedly as GFR falls, and the half-life is prolonged.

Postoperative acute kidney injury

Postoperative acute kidney injury (AKI) is a severe condition in critically ill patients in which drug excretion is impaired.

01

Precipitating factors for AKI

Common perioperative conditions such as major surgery, massive blood loss, sepsis, and hypotension can all trigger acute kidney injury.

02

Markedly impaired drug excretion

In AKI, tubular secretion and reabsorption are also impaired, further increasing the risk of drug accumulation; dosing regimens must be adjusted promptly.

03

Body temperature and acid–base balance

Hypothermia can reduce renal blood flow and tubular function; acidosis may alter the degree of drug ionization, affecting its tubular reabsorption.

Typical PK change patterns

The final common outcome of perioperative pharmacokinetic changes.

1

Distribution changes are the most pronounced

Dramatic fluctuations in blood volume, protein binding, and tissue perfusion cause large swings in the apparent volume of distribution (Vd).

2

Metabolism generally slows

Reduced hepatic perfusion, hypothermia, and inflammatory responses act together to produce an overall decrease in hepatic drug clearance (CL).

3

Excretion is readily impaired

Inadequate renal perfusion and a high risk of postoperative AKI delay renal drug excretion, prolonging the elimination half-life (t1/2).

4

Final common outcome

Drug effects last longer in the body, sensitivity increases, and the risks of accumulation and adverse reactions rise markedly.

Key clinical medication takeaways

Based on perioperative patterns of PK changes, guide clinical medication practice.

01

Reduce the induction dose

For patients with hypovolemia or older adults, induction anesthetics should be given at reduced doses and administered slowly to avoid marked hemodynamic fluctuations.

02

Adjust the maintenance dose

Because metabolism and excretion are slowed, the maintenance dose may need to be reduced or the dosing interval extended to avoid drug accumulation.

03

Strengthen therapeutic drug monitoring

For drugs with a narrow therapeutic window—such as neuromuscular blocking agents, analgesics, and aminoglycoside antibiotics—therapeutic drug monitoring should be strengthened.

04

Pay attention to special populations

In older adults, patients with obesity, shock, or hepatic/renal insufficiency, pharmacokinetic changes are more pronounced; a more refined individualized dosing regimen is required.

Thank you!