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Review Article

Review of the Evidence on Preventing and Managing Acute Kidney Injury after Cardiac Surgery with Amino Acids

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ABSTRACT

Background: Acute kidney injury (AKI) after cardiac surgery leads to serious outcomes, including higher mortality and increased risk of chronic kidney disease. The pathophysiology includes hemodynamic changes, inflammation, and direct renal damage. Key risk factors are chronic kidney disease, older age, diabetes, hypertension, and surgical issues like cardiopulmonary bypass (CPB) and nephrotoxic agents. CPB can cause inflammation, worsening renal blood flow and glomerular filtration rate (GFR). Preventing AKI requires a comprehensive approach that encompasses preoperative optimization, intraoperative management, and postoperative care. Important strategies include optimizing the CPB circuit, using blood cardioplegia for better myocardial and renal protection, and managing fluid balance. This study aimed to examine the factors leading to acute kidney injury during heart surgery and to identify strategies for addressing it.

Methods: Research articles from information sources and databases over the past five years were analyzed using keywords. The studies were classified and summarized according to the disease's pathophysiology and management strategies and clinically evaluated. The findings were assessed based on clinical evidence and compiled into a review article.

Results: Amino acids are essential for renal protection, as they enhance blood flow, improve GFR, scavenge reactive oxygen species (ROS), modulate inflammation, support cellular energy, inhibit apoptosis, aid in protein synthesis, and maintain renal autoregulation. Specific amino acids, including L-Arginine, L-Citrulline, L-Carnitine, Taurine, L-Glutamine, L-Cysteine, L-Methionine, L-Ornithine, L-Tyrosine, and Branched-Chain Amino Acids (BCAAs), have demonstrated protective effects. These amino acids can enhance postoperative GFR and potentially lower the risk of AKI by bolstering renal functional reserve and stimulating local renal growth factors.

Conclusion: A comprehensive strategy incorporating preoperative, intraoperative, and postoperative measures, along with the judicious use of amino acids, is essential for preventing AKI and improving outcomes in patients undergoing cardiac surgery.

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Introduction

Acute kidney injury (AKI) following cardiac surgery is associated with adverse outcomes, including higher mortality, increased postoperative complications, and elevated rates of progressive chronic kidney disease. AKI in the context of cardiac surgery refers to a sudden and often temporary decline in kidney function that occurs after a cardiac surgical procedure. This condition is a common complication following cardiac surgery and can range from mild to severe, potentially leading to the need for renal replacement therapy, such as hemodialysis [1-3].

Hemodynamic changes can result in "functional" AKI after cardiac surgery, characterized by an acute decline in glomerular filtration rate (GFR) without significant tubular cell injury. This type of AKI generally carries a lower risk of adverse outcomes compared to AKI with significant tubular injury. Evidence suggests that a major problem in cardiac surgery is apparent tubular injury in AKI, as indicated by various damage biomarkers [1-4].

Clinical manifestations

AKI in cardiac surgery patients can be identified by several early signs that healthcare providers should monitor closely. Key indicators include a significant decrease in urine output, defined as less than 0.5 mL/kg/hour for six hours, which suggests reduced kidney function. Elevated serum creatinine levels, either an increase of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours or a rise to ≥1.5 times the baseline level within the past week, are important AKI biomarkers. Electrolyte imbalances, especially hyperkalemia, can cause cardiac arrhythmias. Fluid overload may present as edema, pulmonary congestion, or weight gain due to fluid retention. Changes in mental status, such as confusion, lethargy, or agitation, can stem from uremia due to waste product accumulation. Gastrointestinal symptoms like nausea, vomiting, and anorexia may arise from toxin buildup and electrolyte disturbances. Increased fatigue and weakness often result from the body's impaired ability to eliminate waste and manage fluid and electrolyte balance [3-6].

Methods

Definitions and classification

The definition of AKI is primarily based on alterations in serum creatinine levels and urine output, as detailed in various clinical guidelines and consensus definitions, including the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [4]. According to these guidelines, AKI is diagnosed when any of the following criteria are met within a 48-hour period:

1. A rise in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L).
2. An increase in serum creatinine to ≥1.5 times the baseline level, which is known or presumed to have occurred within the past seven days.
3. A urine volume of <0.5 mL/kg/hour for 6 hours.

The severity of AKI is categorized into stages based on the degree of increase in serum creatinine or the duration of oliguria, ranging from Stage 1 (the least severe) to Stage 3 (the most severe) [4-5].

The severity of AKI in cardiac surgery patients is assessed using standardized criteria from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which are based on serum creatinine levels and urine output. AKI severity is classified into three stages:

- Stage 1: Serum creatinine increases by ≥0.3 mg/dL or ≥1.5 times baseline within 7 days, or urine output <0.5 mL/kg/hour for 6-12 hours.
- Stage 2: Serum creatinine increases ≥2 times baseline, or urine output <0.5 mL/kg/hour for 12-24 hours.
- Stage 3: Serum creatinine increases by ≥3 times baseline or ≥4.0 mg/dL, or urine output <0.3 mL/kg/hour for 24 hours, or anuria for 12 hours.

Management implications vary by stage:

- Stage 1: Close monitoring of kidney function, adjustment of nephrotoxic medications, adequate hydration, and management of electrolyte imbalances.
- Stage 2: In addition to Stage 1 measures, more aggressive fluid and electrolyte management may be necessary, with consideration for renal dose dopamine or vasopressors to improve renal perfusion. Dialysis is usually not indicated unless significant electrolyte abnormalities or fluid overload occur.
- Stage 3: This stage requires intensive management, including renal replacement therapy (RRT) such as hemodialysis or continuous renal replacement therapy (CRRT), along with ICU admission for close monitoring of complications like hyperkalemia, metabolic acidosis, and fluid overload. Nutritional support and careful medication management are also critical [3-5].

Early recognition and prompt management are essential at all stages to prevent further kidney damage and improve outcomes, necessitating collaboration among the surgical team, nephrologists, and other specialists for comprehensive care [4, 6].

Predisposing factors and risk factors

Several risk factors contribute to the development of AKI in the context of cardiac surgery, which can be broadly categorized into patient-related, surgical, and perioperative factors. Patient-related factors include pre-existing chronic kidney disease (CKD), advanced age, diabetes mellitus, hypertension, anemia, dehydration or volume depletion, obesity, and genetic predisposition [1, 3, 7]. Surgical factors encompass the type of surgery, duration of surgery, use of cardiopulmonary bypass (CPB), aortic cross-clamp time, and hemodilution. Perioperative factors include intraoperative and postoperative hypotension, use of nephrotoxic agents, sepsis, hypovolemia, contrast-induced nephropathy, and acute tubular necrosis (ATN). Additionally, genetic predisposition and the inflammatory response triggered by surgical trauma and CPB can affect renal function. Cardiopulmonary bypass (CPB) is a known cause of AKI, as it can affect renal perfusion and trigger inflammation [1, 3, 8].

Pathophysiology

CPB activates the complement system, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines can cause a cascade of inflammatory reactions that affect kidneys. The inflammatory response can lead to endothelial dysfunction, characterized by increased vascular permeability and reduced vasodilation, resulting in renal hypoperfusion and decreased glomerular filtration rate (GFR). Inflammatory cytokines and chemokines can activate leukocytes, leading to their infiltration into the renal tissue. Activated leukocytes can release reactive oxygen species (ROS) and proteases that damage renal tubular cells. The inflammatory response can also activate the coagulation cascade, leading to the formation of microthrombi in the renal vasculature, compromising renal blood flow. The inflammatory response can disrupt the normal autoregulation of renal blood flow, leading to reduced renal perfusion and GFR. [3, 5, 8-10].

Preventing AKI from cardiac surgery requires a holistic strategy encompassing preoperative optimization, intraoperative management, and postoperative care. Preoperative management includes risk assessment, managing comorbidities, avoiding nephrotoxins, and maintaining hydration [11]. In surgery, ensuring hemodynamic stability, optimizing the CPB circuit, providing appropriate cardioplegia, and controlling temperature are crucial. To reduce the risk of AKI during CPB, key strategies focus on minimizing renal hypoperfusion, ischemia, and inflammation. Optimizing the CPB circuit with lower priming volume and blood cardioplegia enhances protection for both the heart and kidneys [12-13]. The type of cardioplegia solution used during CPB significantly influences renal protection and the risk of AKI. Blood cardioplegia, which combines a crystalloid solution with the patient's own blood, offers superior oxygen-carrying capacity and buffering effects, maintaining better oxygenation of the myocardium and renal tissue. It also reduces the inflammatory response and provides overall better myocardial and renal protection, thereby lowering the risk of AKI [3, 5]. In contrast, crystalloid cardioplegia, while simpler and more cost-effective, lacks the oxygen-carrying capacity of blood, has limited buffering capacity, and can contribute to hemodilution, potentially compromising renal function. Del Nido cardioplegia, a specialized crystalloid solution designed for longer-lasting myocardial protection, may reduce metabolic demand and hemodilution but has limited data on its direct impact on renal protection and AKI risk [7-9, 14]. Effective hemodynamic management ensures proper perfusion pressure, while fluid management prevents hypovolemia and overload. Managing hemodilution by maintaining normothermia or mild hypothermia is essential for renal function. Pulsatile flow may enhance renal perfusion, though its benefits are debated. Avoiding nephrotoxic agents, reducing cross-clamp time, and considering early renal replacement therapy for AKI are crucial [15-16]. Ischemic preconditioning may mitigate AKI risk, while the efficacy of pharmacological agents like N-acetylcysteine (NAC), statins, and low-dose dopamine remains uncertain and requires further study. Postoperatively, it’s essential to monitor hemodynamics, manage fluids and electrolytes, recognize complications early, and consider renal protective measures [17-18].

Prevention and management

Research indicates that applying a protein load increases the GFR, suggesting a functional physiological reserve within nephrons. This reflects the kidneys' ability to enhance filtering capacity in response to higher protein intake and during periods of increased metabolic demand or intrinsic kidney disease, primarily through increased renal plasma flow from vasodilation in preglomerular arterioles [8]. Protein load administration may help recruit this renal functional reserve and offer renoprotection [4-6]. It seems that amino acid infusion improves postoperative GFR and potentially reduces the risk of AKI related to cardiac surgery. The increase in GFR in response to protein intake is partly due to the renal tubules' ability to adapt to different dietary protein levels. This adaptability is essential for maintaining homeostasis, especially in patients with impaired renal function [1, 3]. Research indicates that specific amino acids, like arginine and leucine, significantly enhance renal perfusion and influence the expression of renal transporters, which are crucial for reabsorbing nutrients

and electrolytes, thus supporting overall kidney function [6-7]. Evidence indicates that optimizing amino acid availability during the perioperative period can improve nitrogen balance and mitigate catabolism effects, especially in those undergoing major surgeries [1, 3, 10]. Research shows that continuous administration of a balanced amino acid mixture is beneficial, with a recommended dose of 2 g/kg/day of ideal body weight, capped at a maximum of 150 grams daily. This regimen should commence upon admission to the operating room and continue consistently for up to 72 hours post-infusion or until ICU discharge. If enteral or parenteral nutrition is initiated within the first 72 hours, the amino acid mixture dosage should be adjusted to maintain the total intake at 2 g/kg/day, considering dietary sources of amino acids [5-6, 8].

The decreased incidence of AKI is linked to both the protective properties of amino acids and their ability to stimulate local renal growth factors, which may enhance cellular repair mechanisms in the kidneys, thereby boosting resilience to stressors encountered during and after surgery [14, 17].

The protective effects of amino acids on the nephron during cardiac surgery involve several key physiological processes. Amino acids can enhance renal blood flow by dilating renal arteries, ensuring better oxygen and nutrient delivery to the renal tubules. They can also improve the GFR by modulating renal hemodynamics [3, 11]. Additionally, amino acids possess antioxidant properties, scavenging reactive oxygen species (ROS) and reducing oxidative stress. They can modulate the inflammatory response by inhibiting pro-inflammatory cytokines and chemokines. Amino acids are crucial for cellular energy production, supporting the synthesis of adenosine triphosphate (ATP) and preserving cellular function. They can inhibit apoptosis in renal tubular cells, maintaining structural and functional integrity. Amino acids also support protein synthesis, aiding in repair and regeneration after surgery. Furthermore, they help maintain the normal autoregulation of renal blood flow, protecting the kidneys from hypoperfusion or hyperperfusion injuries, and regulating renal autoregulation. These mechanisms collectively help preserve renal function and integrity, reducing the risk of AKI [4-5, 11, 13].

Discussion

Several amino acids have been identified for their protective effects on the nephron during cardiac surgery. The most effective include L-Arginine, L-Citrulline, L-Carnitine, Taurine, L-Glutamine, L-Cysteine, L-Methionine, L-Ornithine, L-Tyrosine, and Branched-Chain Amino Acids (BCAAs). These amino acids protect the nephron through various mechanisms. Both L-Arginine and L-Citrulline enhance renal blood flow during cardiac surgery by increasing the production of nitric oxide, which leads to vasodilation of the renal arteries. This improves oxygen and nutrient delivery to the renal tubules, protects against ischemia and hypoxia, and can improve glomerular filtration rate by modulating renal hemodynamics. These effects are crucial for maintaining renal function and integrity during and after cardiac surgery [14, 16-17].

L-Carnitine, Taurine, L-Glutamine, L-Cysteine, L-Methionine, L-Ornithine, and L-Tyrosine play crucial roles in protecting the nephron during cardiac surgery. L-Carnitine supports energy metabolism by facilitating the transport of fatty acids into the mitochondria for beta-oxidation, thereby ensuring adequate ATP production and scavenging ROS to reduce oxidative stress. Taurine acts as a powerful antioxidant, scavenging ROS and stabilizing cell membranes to protect against ischemia-reperfusion injury. L-Glutamine serves as a major energy source for renal cells, supporting ATP production and acting as a nitrogen donor for protein synthesis and repair. L-Cysteine is a precursor to glutathione, scavenging ROS and protecting the nephron from oxidative damage. L-Methionine also scavenges ROS and donates sulfur for antioxidant synthesis. L-ornithine detoxifies ammonia through the urea cycle and may have antioxidant and anti-inflammatory effects. L-Tyrosine is a precursor to dopamine, which dilates renal blood vessels and enhances renal blood flow, protecting against ischemia [2, 14, 16-17].

Conclusions

Acute kidney injury is a significant concern in managing cardiac surgery patients due to its frequency and complications. Effective prevention and intervention strategies can improve patient recovery and prognosis. The strategic application of protein and amino acid supplementation in clinical settings can optimize the kidneys' functional reserve and offer a promising approach to preventing renal injury. By implementing these targeted strategies, healthcare providers can reduce the risk of AKI during CPB, leading to better patient outcomes. It remains unclear if the reduction in AKI incidence after amino acid infusion truly indicates a protective effect on renal tubules or is influenced by other clinical factors. Therefore, ongoing research is needed to clarify the underlying mechanisms and to develop tailored guidelines for protein intake, particularly for those at higher risk of renal complications. This exploration is vital for improving kidney health and preventing injury in vulnerable patients.

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