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Review

Pulmonary Ischemia-Reperfusion Injury

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ABSTRACT

Pulmonary ischemia-reperfusion (I/R) injury is recognized as a key factor in the development of primary graft dysfunction and remains a major cause of perioperative morbidity and mortality in both lung transplantation and thoracic surgical procedures. This type of injury encompasses several pathological mechanisms, including oxidative stress, inflammation, and fibrosis. Literature indicates that I/R injury begins with tissue hypoxia, reperfusion-induced oxidative stress is closely linked to disruption of the endothelial barrier, contributing to early edema formation and impaired pulmonary compliance. Followed by the excessive generation of reactive oxygen species, and further progresses through an amplified inflammatory response. These observations highlight the essential role of antioxidants in both preventing and managing I/R injury across various tissues and organs.

Keywords: Antioxidant, pulmonary ıschemia, reperfusion

INTRODUCTION

Ischemia-reperfusion (I/R) injury refers to secondary organ and tissue damage that occurs following the restoration of blood flow (reperfusion) to ischemic tissue.[1] Ischemia, in contrast, refers to a state in which issue blood flow is partially diminished or entirely halted by various underlying factors, leading to an inadequate delivery of molecular oxygen (O^2) or a complete absence of oxygen within the affected tissues.[2] As is well known, I/R injury can occur in nearly all organs and tissues.[3] The sequence of ischemia followed by reperfusion can occur during numerous surgical interventions, such as lung transplantation.[4] Notably, pulmonary I/R injury is regarded as a leading factor in the development of primary graft dysfunction after lung transplantation and remains a significant contributor to perioperative morbidity and mortality in thoracic surgical practice.[5] It is well established that reperfusion causes more severe tissue damage than ischemia alone.[6] Matrix remodeling, angiogenesis, and fibrosis.[7]

Neutrophil-mediated inflammatory amplification further accelerates epithelial and microvascular injury, influencing postoperative respiratory outcomes. The primary mechanism underlying reperfusion injury is related to the reoxygenation that occurs during reperfusion. During this process, the xanthine oxidase accumulated throughout ischemia converts hypoxanthine to xanthine in the presence of an excessive supply of O^2, leading to the generation of abundant reactive oxygen species (ROS).[6,8] ROS, which act as key mediators during reperfusion, attack membrane lipids and promote the generation of harmful lipid peroxidation products, including aldehydes and malondialdehyde.[6] Among the most extensively studied ROS are the superoxide anion (O^2), hydroxyl radical, hydrogen peroxide, hypochlorous acid, and peroxynitrite, which is derived from nitric oxide.[2] In lung tissue, excessive ROS generation occurs both during ischemia and following reperfusion.[9] Endothelial cells and type II pneumocytes play a major role in the generation of ROS in the lungs. Moreover, the mechanisms of oxidative injury induced by ischemia and hypoxia in the lungs are known to differ from each other.[3] It has been proposed that oxidative stress during pulmonary ischemia can occur independently of adenosine triphosphate depletion.[3,10]

Another mechanism of I/R injury involves the increase in intracellular calcium levels during ischemia, which activates phospholipase A_2. This activation enhances the production of arachidonic acid from membrane phospholipids, leading to the activation of cyclooxygenase-2 (COX-2) and the subsequent release of proinflammatory prostaglandins and reactive oxygen

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species (ROS). Pharmacologic strategies, including antioxidant therapy and modulation of inflammatory signaling pathways, are increasingly being explored to mitigate pulmonary dysfunction.

As evidenced by the literature, I/R injury is a pathological condition initiated by a lack of oxygen in the tissue, progresses with the generation of ROS, and expands through inflammatory responses.[6] Therefore, the treatment of pulmonary I/R injury requires an integrated and multidisciplinary approach encompassing surgical, anesthetic, and pharmacological strategies.[5] It has been suggested that antioxidant therapy may be beneficial in preventing tissue damage caused by increased oxidant production. Protective ventilation approaches and controlled reperfusion techniques have demonstrated promise in reducing perioperative lung injury.

Antioxidants not only inhibit the formation of free radicals but also contribute to the recovery of tissues affected by oxidative damage, neutralize reactive intermediates, and promote the reduction of oxidized biomolecules.[11] Consequently, while oxidant parameters increase during I/R injury in various tissues and organs, antioxidant parameters tend to decrease. This indicates that antioxidants play a very important role in the prevention and treatment of tissue and organ I/R injury.

MAIN POINTS

- Pulmonary ischemia-reperfusion injury represents a major pathophysiological mechanism underlying primary graft dysfunction in lung transplantation and remains a critical determinant of perioperative clinical outcomes.
- Excessive generation of reactive oxygen species during reperfusion initiates a cascade of oxidative and inflammatory events, leading to structural and functional deterioration of pulmonary tissue.
- A coordinated approach integrating surgical refinement, anesthetic optimization, and targeted antioxidant strategies is essential for mitigating pulmonary ischemia-reperfusion-associated tissue injury.

Ethics

Informed Consent: N/A.

Footnotes

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