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Role of Endothelin-1 on Myocardial Ischemia-Reperfusion Injury: A Comprehensive Review

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ABSTRACT

Background: Effective management of acute myocardial infarction (AMI) relies on the swift restoration of coronary blood flow, yet a significant portion of the myocardium remains underperfused due to ischemia-reperfusion injury (IRI), which is exacerbated by factors such as elevated endothelin-1 (ET-1) levels. The balance between relaxation factors like nitric oxide (NO) and contractile factors is crucial for vascular homeostasis, and any dysregulation in this system can lead to increased myocardial damage and contribute to cardiovascular diseases. Objective: To investigate the impact of endothelin on ischemia-reperfusion injury. Method: The approach adopted is a review of existing literature. This study was designed as a systematic review with a narrative approach to provide ET-1 mechanisms and its contribution to ischaemia-reperfusion myocardial injury. Results: The research indicates that endothelin (ET) plays a significant role in myocardial ischemia and reperfusion, resulting in increased production and release of ET-1. The released ET-1 causes considerable coronary constriction, particularly following ischemia/reperfusion, and may directly contribute to myocardial ischemia while also stimulating neutrophil activation and the formation of free radicals. Studies utilising pharmaceutical agents to block ET-1 actions have demonstrated a decrease in ischemia-reperfusion injury, underscoring the physiological importance of endogenous ET. Nevertheless, conflicting results necessitate further investigation in controlled settings using long-lasting ET receptor antagonists or ET-converting enzyme inhibitors to gain a better understanding of ET's involvement in this scenario. Conclusion: The article highlights that ischaemia and reperfusion significantly influence endothelin (ET) mechanisms, leading to increased production and release of ET-1, which causes coronary constriction and may contribute to ischaemia/reperfusion injury through various pathways. While pharmacological agents targeting ET-1 have shown promise in reducing injury, conflicting results necessitate further research with controlled studies to better understand the role of ET in this context.

Keywords: *Endothelin-1, myocardial ischaemia reperfusion injury, vascular endothelium.*

1. INTRODUCTION

The key to successfully managing acute myocardial infarction (AMI) lies in quickly restoring blood flow to the heart and allowing the heart muscle to regain oxygen [1-3]. Although the blocked artery causing the heart attack is successfully reopened, a considerable amount of the heart muscle in the affected area is still not receiving enough blood flow due to the damage caused by the reperfusion process [4]. This injury is closely associated with the nitric oxide (NO) signaling pathway and its primary enzyme, nitric oxide synthase (NOS) [5,6]. NO plays an essential part in IRI through its functions of controlling blood pressure, causing vasodilation, stopping platelet aggregation, and blocking leukocyte adhesion [5-7]. However, the phenomenon of "no-reflow" can occur even when epicardial blood flow is restored, indicating that reperfusion itself can cause additional damage to cardiomyocytes [8-10]. Factors such as calcium overload, leukocyte infiltration, and free radical generation contribute to this reperfusion injury, while elevated levels of endothelin-1 (ET-1) exacerbate myocardial damage and reduce coronary blood flow [11-13].

The vascular endothelium is essential for maintaining homeostasis through a balance of relaxation factors (RF) and contractile factors (CF), with ET-1 being a significant vasoconstrictor [14-15]. An imbalance in this system can lead to abnormal vasoconstriction and contribute to cardiovascular diseases [16-18]. Recent studies have highlighted the role of NO in regulating ET-1, preventing platelet and leukocyte aggregation, and protecting the vascular endothelium from injury [19]. Under pathological conditions, the protective mechanisms of the endothelium may be compromised, resulting in an imbalance between ET and NO release [19]. This dysregulation can lead to a predominance of CF or altered responses of vascular smooth muscle, ultimately exacerbating myocardial ischemia, hypertension, and other cardiovascular disorders [20]. It is essential to comprehend these interactions in order to create focused treatment plans that can lessen the impact of IRI and enhance results for individuals with AMI.

2. METHODS

This study used a literature review method to explore the role of endothelin-1 (ET-1) in myocardial ischaemia-reperfusion injury. This method aimed to identify, evaluate and synthesise current research findings relevant to the dynamics of ET-1 during ischaemia and reperfusion phases, as well as the potential impact of endothelin receptor antagonists as therapies. This study was designed as a systematic review with a narrative approach to provide a understanding of ET-1 mechanisms and its contribution to ischaemia-reperfusion myocardial injury, based on evidence available in the scientific literature. The data used were obtained from scientific articles published in reputable international journals and indexed in databases such as PubMed, Scopus, ScienceDirect, and Google Scholar. Articles analysed were those that addressed endothelin-1 and its role in myocardial ischaemia-reperfusion injury, as well as the effects of endothelin receptor antagonists in reducing such injury.

The selection criteria for this study involved choosing research articles or meta-analyses that focused on the impact of ET-1 in myocardial ischemia and reperfusion, alongside research on how ET-1 causes vasoconstriction, inflammation, and oxidative stress, and the effectiveness of ET receptor antagonists. Articles selected were published in English and published within the last 10-15 years to ensure relevance to the latest scientific developments. Exclusion criteria included articles that did not have full-text, were limited to abstracts, or were not directly related to myocardial ischaemia-reperfusion and ET-1. Data were collected by using relevant keywords, such as ‘Endothelin-1 and myocardial ischaemia-reperfusion injury,’ ‘coronary constriction during ischaemia/reperfusion,’ and ‘endothelin receptor antagonists in myocardial protection’ in the process of searching articles in the database. Articles that met the selection criteria were then analysed in depth to summarise the key findings supporting the study of ET-1 mechanisms and therapeutic opportunities in myocardial ischaemia-reperfusion injury.

3. RESULTS

Plasma Levels, Release and Production of Endothelin During Ischaemia/Reperfusion

During ischaemia and reperfusion, the production and release of endothelin-1 (ET-1) are significantly increased. This elevation in plasma levels of ET-1 contributes to coronary constriction and may lead to myocardial injury, highlighting its pathophysiological role in these conditions. Further studies are needed to clarify its mechanisms and effects [21, 22]. The dynamics of endothelin-1 (ET-1) during ischaemia and reperfusion are critical in understanding myocardial responses to these conditions [23, 24]. Research indicates that ET-1 levels in the liver tissue and hepatic venous blood show a slight increase during ischaemia, followed by a marked elevation after reperfusion [25]. This suggests that the release of ET-1 is closely linked to the ischaemic and reperfusion phases, potentially exacerbating tissue damage and influencing recovery processes [25].

In the context of myocardial ischaemia and reperfusion, the production and release of ET-1 are notably stimulated. The coronary constrictor response to ET-1 is significantly heightened during these phases, which can lead to adverse effects on myocardial function [26]. The increased levels of ET-1 not only contribute to vasoconstriction but may also have direct pro-ischaemic effects on the myocardium, further complicating the recovery from ischaemia [26-28].

The implications of elevated ET-1 levels during ischaemia/reperfusion extend beyond immediate vascular responses [29]. ET-1 may have an impact on the activation of neutrophils and the generation of oxygen-derived free radicals, potentially contributing to the development of ischaemia/reperfusion injury [30]. It is crucial to comprehend these processes to create treatment plans that can lessen the harmful impacts of ET-1 in medical settings. More studies are needed to investigate how ET receptor blockers and enzyme inhibitors could help decrease damage caused by ischaemia and reperfusion.

Coronary Constrictor Responses to Endothelin-1 Following Ischaemia/Reperfusion

After experiencing a lack of blood flow followed by restoration, the coronary artery's ability to constrict in response to endothelin-1 (ET-1) is greatly increased [31]. The rise in numbers is believed to be caused by the enhancement of ET B receptors in the smooth muscle cells of the coronary artery, resulting in increased vasoconstriction and decreased blood flow to the heart, making the damage to the heart muscle worse [32].

The interplay between ET-1 and nitric oxide (NO) during these phases is complex, as NO can have both protective and

harmful effects[19,23,24]. Elevated ET-1 levels can counteract the vasodilatory effects of NO, further contributing to coronary constriction and potentially worsening ischaemic conditions [14, 19].

Moreover, the production of ET-1 is stimulated during ischaemia, leading to increased vasoconstriction and reduced myocardial perfusion [33]. This response is critical in understanding the pathophysiology of ischaemia/reperfusion injury and highlights the potential for targeting ET-1 pathways in therapeutic interventions [34].

Use of Endothelin Receptor Antagonists in Myocardial Ischaemia/Reperfusion

The use of endothelin (ET) receptor antagonists in studies of myocardial ischaemia and reperfusion has garnered significant attention due to the critical role of endothelin-1 (ET-1) in mediating vasoconstriction and contributing to myocardial injury during these events [35]. ET-1 is a potent vasoconstrictor that is released in response to ischaemia, leading to increased coronary vascular resistance and reduced myocardial perfusion [36]. By blocking the effects of ET-1, receptor antagonists can potentially mitigate the adverse consequences of ischaemia/reperfusion injury, making them a promising therapeutic avenue for improving outcomes in patients with acute myocardial infarction [37, 38].

Research has demonstrated that ET receptor antagonists, such as bosentan and tezosentan, can significantly reduce myocardial injury in experimental models of ischaemia and reperfusion [39, 40]. These antagonists work by inhibiting the action of ET-1 at its receptors, thereby promoting vasodilation and improving blood flow to the myocardium. Studies have shown that administration of ET receptor antagonists prior to or during reperfusion can lead to a reduction in infarct size, improved left ventricular function, and enhanced recovery of myocardial tissue. This suggests that targeting the ET system may provide a protective effect against the damaging consequences of ischaemia/reperfusion.

In addition to their direct effects on coronary vasculature, ET receptor antagonists may also exert beneficial effects by modulating inflammatory responses associated with ischaemia/reperfusion injury. ET-1 has been linked to increasing the activation of neutrophils and the secretion of inflammatory cytokines, which could worsen damage to the heart [38,39,41]. By blocking ET-1 signaling, receptor antagonists may help to attenuate the inflammatory response, thereby further protecting the myocardium during the critical phases of ischaemia and reperfusion. This dual action—improving blood flow and reducing inflammation—highlights the potential of ET receptor antagonists as a multifaceted therapeutic strategy [41, 42].

Despite the promising results from preclinical studies, the clinical application of ET receptor antagonists in myocardial ischaemia and reperfusion remains an area of ongoing investigation. While some clinical trials have shown beneficial effects, others have yielded mixed results, underscoring the need for further research to optimize treatment protocols and identify patient populations that may benefit most from this therapeutic approach [37, 39, 40]. Future studies should focus on elucidating the precise mechanisms by which ET receptor antagonists exert their effects, as well as exploring their potential in combination with other therapeutic modalities to enhance myocardial protection during ischaemia and reperfusion events.

Mechanism of Action of Endothelin Antagonist

Endothelin (ET) antagonists exert protective effects against ischaemia/reperfusion injury through multiple mechanisms, primarily by blocking the action of endothelin-1 (ET-1), a potent vasoconstrictor [43]. During ischaemia, ET-1 levels rise significantly, leading to increased vascular resistance and reduced coronary blood flow, which can exacerbate myocardial injury [40, 43]. By inhibiting ET-1 at its receptors, ET antagonists promote vasodilation, thereby enhancing blood flow to the myocardium[39, 40]. This improved perfusion is crucial for delivering oxygen and nutrients to the heart tissue, which is essential for recovery following ischaemia.

In addition to their vasodilatory effects, ET antagonists also play a role in modulating inflammatory responses associated with ischaemia/reperfusion injury. ET-1 has been shown to activate neutrophils and promote the release of pro-inflammatory cytokines, which can contribute to further myocardial damage [43]. By blocking ET-1 signaling, ET antagonists can reduce neutrophil activation and the subsequent inflammatory cascade, thereby limiting the extent of tissue injury [43]. This anti-inflammatory effect is particularly important, as excessive inflammation can lead to additional complications and hinder the healing process in the myocardium [37, 38, 43].

Furthermore, ET antagonists may also influence cellular signaling pathways that are activated during ischaemia/reperfusion. For instance, they can help mitigate oxidative stress by reducing the production of reactive oxygen species (ROS) that are often generated in response to ET-1 [44, 45]. By decreasing oxidative stress, ET antagonists can protect cardiomyocytes from apoptosis and necrosis, further preserving myocardial function. Overall, the multifaceted mechanisms of action of ET antagonists—ranging from improved blood flow and reduced inflammation to decreased oxidative stress—underscore their potential as a therapeutic strategy for protecting the heart during ischaemia/reperfusion events [44-46].

Future Direction Role of Endothelin in Ischaemia/Reperfusion

Future research on endothelin and myocardial ischemia-reperfusion injury is likely to focus on the development of more selective endothelin receptor antagonists that can minimize side effects while maximizing therapeutic benefits. Additionally, exploring the role of endothelin in various cellular signaling pathways and its interaction with other mediators of ischemia-reperfusion injury could provide deeper insights into potential treatment strategies[47]. Investigating the long-term effects

of endothelin antagonism on myocardial recovery and function post-injury will also be crucial. This includes studying the impact of endothelin modulation on cardiac remodeling and the potential for improving outcomes in patients with chronic ischemic heart disease [44, 47].

Moreover, integrating advanced technologies such as gene editing and personalized medicine approaches may enhance our understanding of individual responses to endothelin-targeted therapies [47]. This could lead to tailored treatment plans that optimize the management of myocardial ischemia-reperfusion injury based on specific patient profiles. Future directions in the study of endothelin antagonists and their role in myocardial ischemia-reperfusion injury will likely emphasize the exploration of combination therapies [47, 48]. By integrating endothelin antagonists with other pharmacological agents, researchers aim to enhance the overall efficacy of treatment strategies [48, 49]. This approach could involve pairing endothelin antagonists with anti-inflammatory drugs or agents that target oxidative stress, potentially leading to synergistic effects that further protect myocardial tissue during ischemic events [49].

Another promising avenue for future research is the investigation of biomarkers that can predict the efficacy of endothelin antagonism in individual patients. Identifying specific biomarkers associated with endothelin signaling and myocardial injury could facilitate the selection of patients who are most likely to benefit from endothelin-targeted therapies [50]. This personalized approach may improve clinical outcomes and reduce the risk of adverse effects associated with broader treatment regimens [51].

Finally, the application of novel delivery systems for endothelin antagonists represents an exciting direction for enhancing therapeutic outcomes [51]. Utilizing nanotechnology or sustained-release formulations could improve the bioavailability and targeted delivery of these agents to the myocardium [51]. Such advancements may not only increase the effectiveness of endothelin antagonists but also minimize systemic side effects, paving the way for more effective management of ischemia-reperfusion injury in clinical settings[50,51].

4. CONCLUSION

The results presented in this article clearly show that endothelin (ET) mechanisms are affected by myocardial ischaemia and reperfusion. Specifically, during ischaemia/reperfusion, there is an increase in the production and release of ET-1. This released ET-1 causes significant narrowing of the coronary arteries, which becomes more pronounced after ischaemia/reperfusion. Moreover, it could have direct negative effects on the heart muscle and trigger the activation of neutrophils along with the formation of oxygen-related free radicals. These factors might contribute to the processes that ultimately lead to ischaemia/reperfusion damage. Many research studies have used different medications to block ET-1, including antibodies, enzyme inhibitors, and receptor antagonists. These studies have demonstrated a reduction in ischaemia/reperfusion injury, which implies that ET-1 plays a crucial role in this context. However, conflicting results have made it challenging to interpret these findings, highlighting the need for more research under strict conditions. Using long-acting specific ET receptor antagonists or enzyme inhibitors is essential to understand this fascinating aspect of ET in depth.

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