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Original Article

HBO's Impact on the Prevention and Therapy of Atherosclerotic Heart Disease through Matrix Metalloproteinase-12 (MMP-12) Expression

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ABSTRACT

Background: The utilization and advancement of hyperbaric science continue to evolve, encompassing the investigation of cardiovascular disease. Macrophage activation stimulates the expression of matrix metalloproteinases, specifically MMP-12, which play a crucial role in atherosclerosis by influencing vascular tissue.
Methods: This study aimed to examine MMP-12 expression in cardiovascular disease induced by an atherogenic high-fat diet and explore the effects of hyperbaric oxygen therapy. Previous research has focused on the primary mechanism of hyperbaric oxygen therapy through the SIRT1 (Sirtuin) pathway, which addresses endothelial dysfunction in atherosclerosis treatment. However, the impact of HBO utilization on the treatment and prevention of cardiovascular disease remains unexplored.
Results: Molecular analysis of MMP-12 was conducted using a rat model administered a high-fat diet, followed by HBO treatment. Endothelial dysfunction caused by the high-fat diet was identified as a marker of cardiovascular disease, assessed by endothelin-1 (ET-1) levels. The administration of hyperbaric oxygen (HBO) yielded significant improvements in atherosclerosis and heart disease. The results, with a p-value of 0.05, were significant for both the treatment and prevention of atherosclerotic heart disease in the two groups used as models.
Conclusion: Sprague Dawley rats subjected to hyperbaric oxygen therapy at a pressure of 2.4 ATA, three sessions of 30 minutes each, for ten consecutive days, demonstrated potential for application in cardiovascular disease prevention and treatment.

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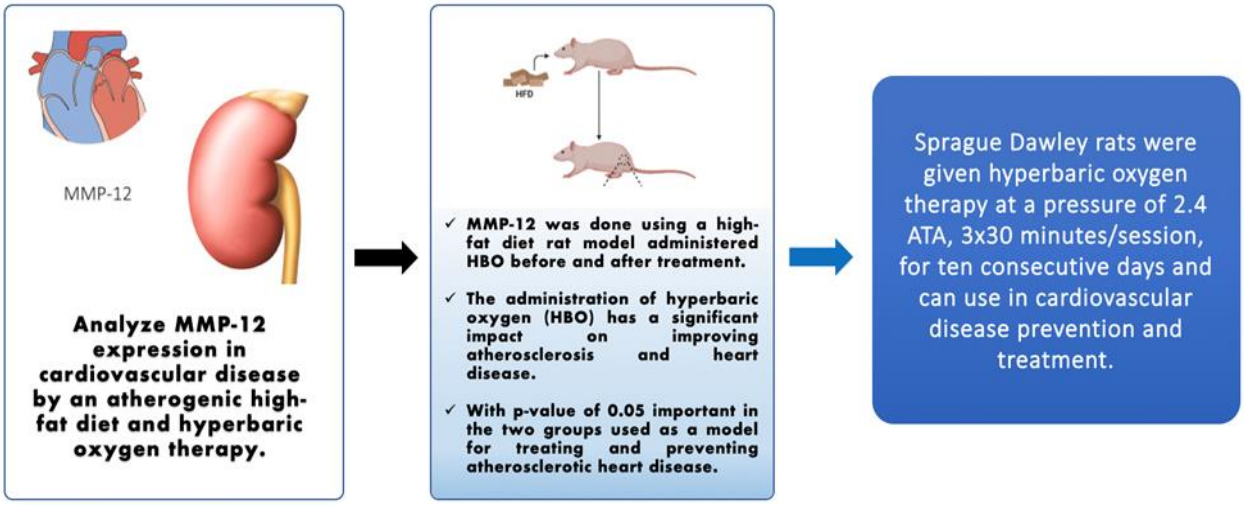
GRAPHICAL ABSTRACT



Introduction

Atherosclerosis, a condition characterized by changes in endothelial cells and the formation of a single layer lining the entire vascular system, is closely associated with the basement membrane in the intima of blood vessels [1].

Endothelial dysfunction is indicated by alterations in the normal functioning of the vascular endothelium. This syndrome is characterized by a pro-inflammatory and prothrombotic state, as well as impaired vasomotor function. Vascular tissue triggers the activation of macrophages, which, in turn, leads to increased expression of matrix metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-12), contributing to endothelial dysfunction [2].

During hyperbaric oxygen therapy, patients inhale 100% oxygen while being exposed to pressures greater than 1 ATA (2.4 ATA) for a specific duration. The underlying principle of hyperbaric oxygen therapy involves the role of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These molecules act as signaling molecules in the transduction cascade for various transcription factors, growth factors, cytokines, and hormones. The beneficial or detrimental effects of these reactive species molecules depend on their concentration and intracellular localization [3].

Atherosclerosis, a prevalent cardiovascular disease in Indonesia, is often initiated by endothelial dysfunction resulting from factors such as hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia, and obesity. As endothelial dysfunction progresses, macrophage activation increases. Excessive macrophage expression can cause damage to blood vessels, attributed to the high production of MMPs by macrophages, including MMP-12, which is associated with plaque rupture in atherosclerosis and originates from vascular endothelial dysfunction. This study aims to investigate the mitigation of endothelial dysfunction through a combination of a high-fat atherogenic diet and hyperbaric oxygen therapy.

There is an urgent need for research in this area, as the findings could contribute to the development of new hypotheses and treatments for coronary heart disease, which is often characterized by narrowing and hardening arteries due to the accumulation of plaque on the blood vessel walls (atherosclerotic heart disease).This study specifically focuses on the role of hyperbaric oxygen therapy in the prevention and treatment of atherosclerotic heart disease in Sprague Dawley rats with endothelial dysfunction, targeting the modulation of activated MMP-12 expression.

Materials and Methods

This study employed an experimental design conducted at the Embryology Laboratory of the Faculty of Veterinary Medicine of Universitas Airlangga, Surabaya. The methodology followed a post-test-only control group design. Ethical approval for the study was obtained from the Commission of Health Research Ethical Clearance of the Faculty of Dental Medicine, Universitas Airlangga, under reference number 380/HRECC, as documented in FORM/IX/2021.

Administration of hyperbaric oxygen

Following the development of endothelial dysfunction after 49 days of a high-fat diet in the treatment group, hyperbaric oxygen therapy was administered for ten consecutive days, consisting of ten sessions. Each hyperbaric oxygen therapy session comprised three 30-minute sessions of pure oxygen gas (approximately 100%) at 2.4 ATA, with 5-minute intervals of air (20-23% oxygen). The ten sessions of hyperbaric oxygen administration were completed within a ten-day period, with a 24-hour interval between each session and the subsequent treatment. In the hyperbaric chamber, a total of 10 rats from the treatment group were exposed to nearly 100% oxygen with P02 98.5%, PCO2 578 ppm, and the temperature of 25 °C.

Results and Discussion

Endothelin-1 (ET-1) levels were measured to identify endothelial abnormalities induced by a high-fat diet. The average levels of endothelin-1 (ET-1) in each group are presented in Table 1. According to the results presented in Table 1, the increase in Endothelin-1 (ET-1) levels was more than twice that of the control group, indicating a significant rise. Endothelin-1 (ET-1) was used as a marker to assess endothelial dysfunction, which was observed at an average level of 9.23 pg/mL. In this study, the average endothelin-1 (ET-1) level was found to be 0.8 pg/mL, demonstrating the presence of endothelial dysfunction and a significant increase in endothelin-1 (ET-1) levels. The study utilized male Sprague Dawley white rats (Rattus norvegicus) aged two months, with a total of 30 rats divided into four treatment groups, each consisting of ten rats. Group 1 (standard control) received a standard diet without hyperbaric oxygen therapy. Group 2 (negative control) was fed a high-fat atherogenic diet without receiving hyperbaric oxygen for seven weeks. Group 3 (treatment group) received the treatment of a high-fat atherogenic diet combined with ten days of hyperbaric oxygen therapy. Group 4 (prevention group) received ten days of hyperbaric oxygen therapy followed by seven weeks of a high-fat atherogenic diet (HBO + atherogenic high-fat diet). After the seven-week period, blood samples were collected from the heart to measure endothelin-1 (ET-1) levels using the ELISA method, confirming the occurrence of endothelial dysfunction in Group 2 (negative control). Following the detection of endothelial dysfunction through the ELISA results, hyperbaric oxygen therapy was administered.

The collected data and subsequent analysis are aligned with the research goals and hypotheses. An ELISA test was conducted to determine the presence of antibodies or antigens in the sample material, specifically focusing on MMP-12 (Table 2). The study results were categorized into four groups: standard control, negative control (high-fat atherogenic diet), treatment group (high-fat atherogenic diet with HBO), and Group 4 (high-fat atherogenic diet followed by ten days of hyperbaric oxygen therapy). After seven weeks, MMP-12 expression was examined. The negative control group (high-fat atherogenic diet) exhibited the highest mean MMP-12 value at 0.436 ng/mL, while the treatment group (HBO therapy) displayed the lowest mean value at 0.246 ng/mL, followed by the prevention group at 0.340 ng/mL.

Table 1: Average levels of endothelin-1 (ET-1) in each group

Variable	G1	G2
Endothelin-1 (ET-1)	0.8 pg/mL	9.23pg/mL

Table 2: Average MMP-12 of each group

Variable	G1	G2	G3	G4
MMP-12 (ng/mL)	0.332 ± 0.029	0.436 ± 0.037	0.246 ± 0.031	0.340 ± 0.029

Significant differences were observed among all the groups (standard control, negative control, treatment group, and prevention group) when assessing the impact of HBO on MMP-12 and ET-1 in the prevention of cardiovascular disease. The ANOVA test yielded a significant difference with a p-value of 0.000 ($p < 0.005$).

In this study, the treatment of endothelin-1 (ET-1) dysfunction induced by a high-fat atherogenic diet was performed using hyperbaric oxygen therapy, which triggers various signaling mechanisms in cells, including MMP-12, known to contribute to the repair of endothelial dysfunction. Hyperbaric oxygen exposure leads to an increase in ROS molecules, which precede the activation of transcription factors, such as NF-κB, in the signaling cascade. However, NF-κB was not specifically investigated in this study. These transcription factors play a crucial role in controlling the expression of genes involved in cellular defense and adaptation, including those encoding antioxidant proteins like heme oxygenase-1 (HO-1) and other proteins like sirtuin (SIRT1).

Endothelial dysfunction is characterized by a disruption in the normal functioning of the vascular endothelium. This syndrome manifests as a pro-inflammatory and prothrombotic state, accompanied by impaired vasomotor function. Vascular tissue activation triggers the activation of macrophages, which, in turn, leads to enhanced expression of matrix metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-12), contributing to endothelial dysfunction [4].

During hyperbaric oxygen therapy, patients receive 100% oxygen inhalation through a mask while being exposed to pressures greater than 1 ATA (2.4 ATA) for a specified duration. The therapeutic effects of hyperbaric oxygen therapy are mediated through the actions of reactive oxygen species (ROS) and reactive nitrogen species (RNS) molecules. These molecules function as signaling molecules in the transduction cascade involving various transcription factors, growth factors, cytokines, and hormones. The beneficial or detrimental consequences of these reactive species depend on their concentration and intracellular localization [3].

The development of atherosclerosis is preceded by endothelial dysfunction, which can be induced by factors such as hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia, and obesity. As endothelial dysfunction progresses, the activation of macrophages increases. Excessive macrophage expression leads to arterial damage, attributed to their high production of MMPs, including MMP-12, which can contribute to plaque rupture in atherosclerosis, starting from vascular endothelial dysfunction. This study aimed to investigate the potential alleviation of endothelial dysfunction through a combination of a high-fat atherogenic diet and hyperbaric oxygen therapy.

Nitric oxide (NO) molecules play a role in endothelial cell regulation through the Extracellular Signal Regulated Kinase pathway and can be released upon administration of hyperbaric oxygen (HBO). Along with MMP-12, proteins such as HO-1, SIRT1, and eNOS act as antioxidants and provide protection against endothelial dysfunction. The molecular effects of hyperbaric oxygen exposure, mediated by increased ROS molecules, impact the activation of the transcription factor NF-κB [5]. Due to the high reactivity of ROS molecules, cells can generate scavenger molecules and antioxidants that maintain redox homeostasis by upregulating genes involved in oxidative stress reduction. ROS molecules induce the expression of pro-inflammatory proteins by activating various transcription factors, including NF-κB [6]. Following HBO exposure, ROS molecules modify adaptive mechanisms that mitigate cell damage [3].

Hyperbaric oxygen exposure triggers signaling processes in cells involving proteins like heme oxygenase-1 (HO-1), Sirtuin-1 (SIRT1), and endothelial nitric oxide synthase (eNOS), which

collectively exert a protective effect on endothelial dysfunction in animal models of endothelial dysfunction. These adaptive proteins play a role in cell protection, particularly in the context of endothelial dysfunction, through a series of signaling events induced by increased ROS molecules resulting from HBO exposure. Antioxidants such as HO-1 and SIRT1 have been identified as cardioprotective proteins [7, 8].

Hydrogen peroxide (H2O2) constitutes the majority of ROS generated during hyperbaric oxygen therapy (HBO) [3]. In the presence of ROS, cells do not necessarily undergo cell death. Cells possess a scavenger enzyme system that includes superoxide dismutase (SOD), which converts hydrogen peroxide (H2O2) into water and oxygen, thereby preventing ROS-induced damage [9].

The administration of HBO should carefully consider the dosage and interval of administration, as the appropriate dosage is crucial. Excessive elevation of ROS molecules can impede adaptive capacity of the cells to counteract the excess free radicals, resulting in a state of oxidative stress that may have detrimental effects on cells [8].

The concept of hormesis, preconditioning hypoxia, and redox theories serve as the primary mechanisms underlying hyperbaric oxygen therapy (HBO).

1. The redox process involves utilizing the generated ROS.
2. Hormesis: The dose of oxidants under stress is related to the production of H2O2, with an optimal range of oxidant eustress between 0 and 10 nanomolar. Hormesis therapy employs a dose within the adaptive response range of 10 to 100 nanomolar. Doses exceeding 100 nanomolar should be avoided as they can induce oxidative stress. However, it should be noted that the optimal dosage may vary depending on the specific disease and the microenvironment in which it occurs.
3. Hypoxia preconditioning: This mechanism functions similarly to hypoxia-inducible factor 1-alpha (HIF-1α), although its response can be modified based on the specific microenvironment [9].

Superoxide dismutase (SOD), catalase, and other antioxidant proteins that function as scavengers to counteract elevated levels of free radicals in cells were not specifically examined in this study, nor were other transcription factors such as NF-κB, Activator Protein-1 (AP-1), Interferon Regulating Factor (IRF), and NF-κB. However, these proteins are known to contribute to adaptive cellular responses. The findings of this study suggest that HBO administration can decrease MMP-12 levels in both the treatment and prevention groups, thereby improving endothelial dysfunction in the experimental mice. The balance between oxidants and antioxidants was found to be restored in the body following HBO treatment, highlighting the importance of stimulating and activating antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. These enzymes operate within the window of intervention to reduce oxidative stress (WPOS). This is because cells experience a pseudo-healthy state of oxidative stress, characterized by levels between normal oxidative stress and those generated by disease, which can demonstrate beneficial effects when antioxidants are administered over time [10].

The doses used in this study align with those utilized in previous studies. The concept of hormesis, which proposes that exposure to low doses of potentially harmful substances or environmental factors can induce adaptive beneficial effects on cells or organisms, helps explain the dosage requirement. Different biological responses may be observed at different dosage levels due to the hormetic mechanism. This mechanism involves the activation of receptor kinase- and activating transcription factor-dependent adaptive cellular stress response pathways, leading to the production of cytoprotective proteins such as antioxidant enzymes, chaperone proteins, and growth factors [11].

Following hyperbaric oxygen (HBO) administration, reactive nitrogen species (RNS) and reactive oxygen species (ROS) levels are increased. Hydrogen peroxide (H_2O_2), as a reactive oxygen species (ROS), is subsequently converted into water (H2O) by enzymes such as catalase and glutathione peroxidase [3]. In

addition to prevent oxygen toxicity, the inclusion of air breaks (intervals) of 5 minutes during HBO therapy creates a relatively hypoxic environment, leading to ischemic preconditioning. The switch from pure oxygen to regular air induces a state of apparent hypoxia, as reflected by the decrease in oxygen saturation to 1.01. This apparent hypoxic state activates the transcription factor hypoxia-inducible factor 1 (HIF-1), which serves as a cellular stress response adaptive mechanism. As a result, the oxygen saturation increases to 5.39 at a pressure of 2.4 ATA [7].

When a person is in a pressurized room (hyperbaric chamber) and subjected to a pressure of up to 2.4 ATA, the partial pressure of oxygen (pO2) increases tenfold, leading to a tenfold rise in the oxygen concentration in the blood compared to the expected level. The administration of hyperbaric oxygen (HBO) therapy at a pressure of 2-3 ATA with intermittent oxygen delivery is crucial to prevent oxygen poisoning. In this condition, all body fluids, including blood, lymph, and cerebrospinal fluid, are saturated with oxygen. Oxygen can reach bones and soft tissues that red blood cells cannot access, enhancing the function of white blood cells. It also promotes the formation of new capillaries (neovascularization) and peripheral blood vessels, thereby facilitating a rapid healing process [3].

HBO treatment increases oxygen transport to tissues through two processes. Firstly, there is a 20.1% increase in hemoglobin saturation. Only a small fraction (3%) of oxygen in the blood exists in the dissolved form, while the majority is bound to hemoglobin and transported through plasma fluid. Oxygen in its dissolved form is crucial in this therapy as tissues can readily absorb it via direct diffusion, as opposed to oxygen bound to hemoglobin [12].

The effect of hyperbaric oxygen therapy on the expression of activated MMP-12 in experimental animals with endothelial dysfunction was examined. MMP-12 is part of a large group of enzymes known as matrix metalloproteinases (MMPs), which are zinc-dependent endopeptidases responsible for tissue remodeling and the breakdown of various extracellular matrix components, including collagen, elastin, gelatin, matrix glycoproteins, and proteoglycans [4].

MMPs have the ability to break down all extracellular matrix proteins, as well as several bioactive compounds. They cleave cell surface receptors and release apoptotic ligands (such as FAS ligands), inactivate chemokines and cytokines, and can influence various cellular behaviors, including proliferation, migration, adhesion, differentiation, angiogenesis, and apoptosis [13]. MMPs play a crucial role in tissue healing, physiological processes like morphogenesis and angiogenesis, as well as in the treatment of tissue endothelial dysfunction. The cleavage of ECM proteins by MMPs affects cellular signaling and function. By degrading structural elements of the extracellular matrix, such as collagen, elastin, fibronectin, and laminin, which are part of the fibrous and adhesive components of the ECM, MMPs facilitate cell migration. Dysregulation of the MMP/TIMP balance is implicated in various disorders, including endothelial dysfunction and cardiovascular diseases, both acute and chronic [4].

MMPs possess a signal peptide directing their secretion or insertion into the plasma membrane, followed by a prodomain, a zinc-binding catalytic domain, a hemopexin domain that facilitates interactions with specific substrates and enzymes, and a hinge region that connects the catalytic and hemopexin domains. Based on substrate specificity, domain organization, and circuit equations, MMPs are broadly classified into six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other MMPs with transmembrane domains [14].

MMPs are secreted by various cell types, including connective tissue cells and proinflammatory cells such as lymphocytes, macrophages, neutrophils, endothelial cells, and fibroblasts. MMPs can be activated *in vitro* by different processes, including chaotropic substances and other proteases. In the body, MMPs are initially produced as zymogens and require external activation. Most MMPs are activated outside the cell by serine proteinases or other MMPs [15].

In the context of vascular endothelial dysfunction, which triggers inflammation and the release of proinflammatory cytokines and chemokines, MMP-12 plays a unique role in the heart and blood vessels. It stimulates neutrophil proliferation and migration, thereby initiating the healing process. MMP-12 also activates interferon-alpha (IFN-α), which contributes to the repair of endothelial dysfunction. In addition, MMP-12 can promote anti-inflammatory signals and suppress proinflammatory signals [6].

Previous research has identified potential protein targets for MMP-12, allowing it to exert its proteolytic activity on various protein substrates. This proteolytic activity may contribute to its anti-angiogenic effects. Furthermore, it has been observed that MMP-14, although expressed at lower levels than MMP-12 in polarized macrophages, can cleave endoglin, a membrane protein found in monocyte macrophages [16]. The role of endoglin in this context is of particular interest [17-20].

Macrophages play a crucial role in the development of atherosclerosis, which can be triggered by endothelial dysfunction, hypertension, vasculitis, aortic aneurysm, or other vascular disorders [21, 22]. The polarization and accumulation of macrophages in a chronic pro-inflammatory state can lead to significant and irreversible vascular damage, affecting clinical outcomes [23]. Targeting macrophage inflammation may offer therapeutic potential by promoting early resolution of inflammation [24]. However, the mechanisms underlying macrophage-mediated control of the inflammatory response in the vasculature are not fully understood.

Understanding the novel mechanism of macrophage polarization in this context can provide insights into its contribution to vascular inflammation. In a unique association between endothelial cells and pro-inflammatory GM-CSF monocyte-derived macrophages, there is a release of soluble endoglin (sEng), a soluble protein with pro-inflammatory properties, which targets endothelial cells attached to membrane-bound endoglin. This soluble protein can potentially induce endothelial dysfunction in the presence of hypercholesterolemia. The findings suggest that MMP-12 and soluble endoglin (sEng) directly and synergistically impact the pro-inflammatory response of GM-CSF monocyte-derived macrophages [18, 19, 22]. In the context of hypercholesterolemia, the presence of a soluble protein with pro-inflammatory characteristics can also contribute to endothelial dysfunction. The findings highlight the direct and synergistic influence of MMP-12 and soluble endoglin (sEng) on the pro-inflammatory response of GM-CSF monocyte-derived macrophages [16]. Furthermore, higher levels of soluble endoglin (sEng) are observed in inflammation-associated pathologies where MMP-12 levels are elevated [25, 26]. It is worth noting that GM-CSF monocyte-derived macrophage supernatants have MMP-12-dependent inhibitory effects on endothelial tubulogenesis, which support the anti-angiogenic properties of soluble endoglin (sEng). MMP-12 [16, 20] jd [27-30]. This study discovered that hyperbaric oxygen therapy reduced the expression of activated MMP-12 in Sprague Dawley rats with endothelial dysfunction.

In this particular study, the authors did not assess the activity of MMP-1 and MMP-2 enzymes using histopathological techniques. Histopathology refers to the microscopic examination of tissues for detecting any abnormalities or changes at a cellular level.

Conclusion

In conclusion, hyperbaric oxygen therapy or prophylaxis can effectively reduce MMP-12 expression. This therapy involves administering 98% oxygen at a pressure of 2.4 ATA for three sessions of thirty minutes each.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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