Review

Assessment of endothelial function changes following repeated hyperbaric exposure in divers: a comprehensive review

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Abstract

Objectives: Repeated exposure to hyperbaric pressure and decompression during diving induces unique physiological challenges for the cardiovascular system. The vascular endothelium plays a critical role in maintaining vascular homeostasis through regulating vascular tone, nitric oxide (NO) bioavailability, inflammatory responses, and oxidative balance. Previous investigations have shown that acute hyperbaric exposure may impair endothelial function through oxidative stress, inflammatory activation, and intravascular bubble formation; however, the long-term effects of repeated diving exposure on endothelial health remain unclear. Therefore, this review was conducted to summarize current evidence regarding alterations in endothelial function following repeated hyperbaric exposure in divers and to describe the underlying molecular mechanisms involved in endothelial injury and vascular adaptation. This review aimed to evaluate the effects of repeated hyperbaric exposure on endothelial function in divers and to summarize the potential mechanisms associated with endothelial dysfunction and vascular adaptation.

Methods: A comprehensive literature search was performed in PubMed, ScienceDirect, and Scopus databases using combinations of relevant keywords, including "endothelial function," "diving," "hyperbaric exposure," "decompression," "oxidative stress," "endothelial microparticles (EMPs)," "nitric oxide (NO)," and "heat shock proteins (HSPs)." The review focused on human and animal studies that assessed objective markers of endothelial function following hyperbaric exposure or diving activities.

Results: Current evidence indicates that acute hyperbaric exposure and decompression are associated with increased circulating gas bubbles, oxidative stress, inflammatory activation, and transient endothelial dysfunction. Reduced flow-mediated dilation (FMD) and increased endothelial microparticles (EMPs) have been reported following deep and repetitive diving exposures. Experimental studies have demonstrated enhanced oxidative responses after simulated deep dives, including alterations in lipid peroxidation and antioxidant activity. However, repeated diving training may induce adaptive responses, including decreased bubble formation and improved tolerance to hyperbaric stress, without necessarily causing persistent endothelial impairment. These responses appear to involve regulation of NO bioavailability, heat shock protein (HSP) expression, oxidative pathways, and vascular protective mechanisms.

Conclusions: Repeated hyperbaric exposure induces a complex interaction between endothelial stress and physiological adaptation. Although acute diving-related stress may cause temporary endothelial dysfunction, long-term repetitive exposure may promote protective vascular adaptations. Further longitudinal investigations are required to determine the long-term cardiovascular consequences of these adaptations in professional divers.

Keywords: Endothelial function; Diving; Hyperbaric exposure; Decompression; Oxidative stress; Endothelial microparticles; Nitric oxide; Heat shock proteins

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Introduction

Diving has become an increasingly common professional and recreational activity worldwide, leading to growing interest in the potential long-term cardiovascular consequences of repeated hyperbaric exposure. During diving, increased ambient pressure raises the partial pressure of inspired gases, causing increased dissolution of inert gases in body tissues. During ascent, decompression facilitates the elimination of dissolved gases; however, incomplete gas removal may cause intravascular and extravascular bubble formation, which can initiate decompression-related physiological disturbances [1, 2]. For many years, decompression sickness (DCS) was primarily attributed to the mechanical effects of gas bubbles. However, recent evidence indicates that endothelial dysfunction is a key event in the development of decompression-related vascular injury. Gas bubbles not only cause mechanical obstruction but also interact directly with the vascular endothelium, inducing oxidative stress, inflammatory responses, complement activation, and endothelial injury, which collectively contribute to vascular dysfunction [2, 3]. The vascular endothelium is a metabolically active organ that maintains vascular homeostasis by regulating vascular tone, nitric oxide (NO) bioavailability, coagulation, inflammation, leukocyte trafficking, and vascular remodeling. Endothelial dysfunction is characterized by impaired vasodilatory capacity accompanied by pro-inflammatory and pro-thrombotic alterations and is considered an early marker of cardiovascular disease [1]. Several mechanisms have been proposed to explain endothelial injury following hyperbaric exposure. Hyperoxia increases reactive oxygen species (ROS) production, reducing NO bioavailability and impairing endothelium-dependent vasodilation. Additionally, decompression-induced bubbles generate mechanical stress on endothelial cells, activate inflammatory signaling pathways and complement cascades, and promote the release of endothelial microparticles (EMPs), which function as both biomarkers and mediators of endothelial injury. Experimental studies have also demonstrated alterations in heat shock proteins (HSPs) and endothelial nitric oxide synthase (eNOS), suggesting activation of cellular stress-response pathways during repeated diving exposure [1, 4, 6]. Figure 1 summarizes the main molecular mechanisms involved in endothelial dysfunction following hyperbaric exposure. Although numerous studies have investigated acute endothelial responses following single diving exposures, the long-term consequences of repetitive diving remain incompletely understood. Some studies have reported transient impairment of endothelial function immediately after diving, whereas others have suggested that repeated exposure may induce adaptive physiological responses, including reduced bubble formation, improved oxidative balance, and enhanced vascular tolerance to hyperbaric stress [4-6]. Therefore, it remains unclear whether repeated diving exposure results in cumulative endothelial injury or promotes protective vascular adaptation. Previous reviews have primarily focused on decompression sickness, oxidative stress, or individual molecular mechanisms. However, an integrated evaluation of endothelial physiology, molecular signaling pathways, biomarkers, and adaptive responses remains limited. Therefore, a comprehensive synthesis of current experimental and clinical evidence is required to clarify the relationship between repetitive hyperbaric exposure and endothelial health. Accordingly, the objectives of the present review were to: (1) summarize current evidence regarding acute and chronic alterations in endothelial function following repeated hyperbaric exposure; (2) describe the major molecular mechanisms involved in endothelial injury, including oxidative stress, inflammation, nitric oxide signaling, endothelial microparticles, and heat shock proteins; (3) evaluate evidence supporting vascular adaptation following repetitive diving; and (4) discuss the clinical implications and future research priorities related to cardiovascular health in professional and recreational divers.

Materials and Methods

The researchers conducted a comprehensive literature search in the PubMed, Science Direct, and Scopus databases to identify studies evaluating endothelial responses to hyperbaric exposure. The search strategy included the following keywords: ("endothelial function" OR "endothelium") AND ("diving" OR "hyperbaric exposure" OR "decompression") AND ("microparticles" OR "oxidative stress" OR "nitric oxide" OR "heat shock proteins"). The inclusion criteria were studies involving humans and animals that evaluated objective indicators of endothelial function after hyperbaric exposure or diving, and were published in English until December 2024. We excluded review articles, conference abstracts, editorials, case reports, and studies that did not provide objective measures of endothelial outcomes. The researchers screened the retrieved articles for relevance and selected eligible studies based on their methodological quality and relevance to the objectives of this review.

Results

Physiological Basis: Vascular Bubbles and the Endothelium

Repeated hyperbaric exposure during saturation diving results in prolonged exposure to elevated oxygen partial pressures and decompression-induced vascular gas bubbles, both of which play important roles in endothelial dysfunction. During decompression, inert gas bubbles may form within the circulation and interact directly with the vascular endothelium, initiating oxidative stress, inflammatory responses, and vascular injury rather than acting solely as mechanical obstructive agents [2]. Hyperoxia associated with diving increases the production of oxygen species (ROS), leading to oxidative stress, reduced nitric oxide (NO) bioavailability, impaired endothelium-dependent vasodilation, and endothelial dysfunction [2]. Thom and Mazur's hypothesis on endothelial dysfunction suggests that oxidative injury caused by hyperoxia may be the primary trigger for decompression illness. In this process, intravascular bubbles exacerbate endothelial damage through secondary inflammatory and thrombotic mechanisms. [6]. Bubble–endothelium interactions activate complement pathways, stimulate platelet aggregation, and promote the release of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These processes increase vascular permeability, promote microthrombus formation, and contribute to both local tissue injury and systemic manifestations of decompression sickness (DCS) [2]. Experimental evidence further indicates that antioxidant administration may attenuate oxidative stress and preserve endothelial function following diving exposure. Clinical and experimental studies have demonstrated that antioxidant interventions reduce endothelial impairment after hyperbaric exposure, supporting the central role of oxidative stress in diving-related vascular injury [3]. Importantly, asymptomatic ("silent") vascular bubbles are frequently detected after uneventful dives. Although these bubbles do not immediately produce clinical symptoms, repeated exposure may induce cumulative subclinical endothelial injury, potentially contributing to long-term cardiovascular risk in professional divers [2]. Overall, current evidence supports a two-hit model of endothelial injury. First, hyperoxia induces oxidative stress and decreases NO bioavailability, rendering the endothelium more vulnerable. Secondly, decompression-generated bubbles trigger inflammatory, thrombotic, and complement-mediated responses that exacerbate endothelial dysfunction and contribute to the pathophysiology of DCS [2, 6].

Evidence of Acute Endothelial Dysfunction

Experimental evidence demonstrates that endothelial dysfunction develops rapidly following decompression, although its severity depends on breathing gas composition and the magnitude of oxidative stress. In a controlled crossover study, Madden et al. evaluated endothelial function in healthy volunteers after simulated dives breathing either compressed air or 100% oxygen at 283 kPa (equivalent to 18 meters of seawater) for 60 minutes [3]. Endothelial function, assessed using reactive hyperemia peripheral arterial tonometry (RH-PAT), declined significantly after air dives, whereas impairment was not observed following oxygen dives. These findings indicate that decompression from compressed air induces transient endothelial dysfunction under controlled hyperbaric conditions [3]. Analysis of endothelial microparticles (EMPs) further supported endothelial injury occurrence. CD105-positive EMP concentrations increased markedly after air dives but remained unchanged after oxygen dives, suggesting that endothelial damage is closely associated with decompression-related bubble formation rather than hyperoxia alone [3]. In contrast, circulating inflammatory biomarkers, including E-selectin, P-selectin, interleukin-6 (IL-6), and cortisol, showed no significant changes immediately after exposure, indicating that early endothelial impairment may precede measurable systemic inflammatory responses [3]. These findings align with the idea that the mechanical interaction between vascular gas bubbles and the endothelium is a critical early mechanism of endothelial injury [2]. Subsequent studies have shown that both recreational and professional diving can cause temporary reductions in flow-mediated dilation (FMD), increased levels of oxidative stress biomarkers, and impaired vascular reactivity. These findings further confirm acute but largely reversible endothelial dysfunction after exposure to hyperbaric conditions. Collectively, these observations indicate that endothelial injury is an early physiological response to decompression. It may serve as the initial step in the development of vascular complications related to decompression.

Evidence of Vascular Dysfunction in Breath-Hold Diving

Field studies have demonstrated that endothelial dysfunction is not limited to compressed-gas diving but also occurs during repetitive breath-hold diving. In a prospective study of experienced breath-hold divers,

Barak et al. reported a significant reduction in brachial artery flow-mediated dilation (FMD) after repeated deep breath-hold dives. This indicates an acute impairment of endothelial function when compressed gas breathing is absent [1]. The same study demonstrated a significant increase in circulating microparticles after diving, particularly endothelial-derived CD31+/CD41− microparticles and neutrophil-derived CD66b+ microparticles, reflecting both endothelial injury and activation of inflammatory pathways [1]. These findings suggest that repetitive pressure exposure, intermittent hypoxia–reoxygenation, and oxidative stress may contribute to vascular dysfunction independently of inert gas supersaturation [1, 2] The observed impairment in endothelial function aligns with previous findings indicating that oxidative stress and endothelial activation are common biological responses to diving exposure [2–4]. Moreover, endothelial microparticles (EMPs) have emerged as sensitive biomarkers of subclinical vascular injury and may provide valuable tools for monitoring endothelial health in professional and recreational divers [1,3,4]. Overall, current evidence indicates that repetitive breath-hold diving induces transient endothelial dysfunction and vascular activation, supporting the concept that endothelial injury represents a common physiological consequence of repeated diving exposure and may contribute to the long-term cardiovascular effects associated with diving activities [1–4].

Evidence of Adaptation Following Repeated Exposures

Repeated hyperbaric exposure may induce physiological adaptations that reduce susceptibility to decompression-related vascular injury. In a longitudinal study, Pontier et al. evaluated 22 military divers before and after a 90-day diving training program comprising an average of 67 dives [5]. Endothelial function, assessed by post-occlusive skin blood flow and local heating, remained unchanged after the training period, indicating preservation of endothelial function despite repeated hyperbaric exposure [5]. After completing the training program, there was a significant reduction in the formation of vascular bubbles following diving, as indicated by lower Kisman Integrated Severity Score (KISS) values [5]. However, this protective effect declined three months after stopping regular diving, suggesting the adaptive response is reversible and depends on continued exposure [5]. Notably, no participant developed decompression sickness (DCS) during the training period despite measurable bubble formation. These findings suggest that repeated diving may induce physiological acclimatization characterized by reduced bubble formation and improved tolerance to hyperbaric stress rather than persistent endothelial dysfunction [5]. The mechanisms underlying this adaptive response are likely multifactorial. Experimental evidence suggests that repeated exposure may enhance antioxidant defenses, improve nitric oxide (NO) regulation, increase resistance to oxidative stress, and activate cytoprotective pathways, including heat shock proteins (HSPs), thereby preserving endothelial integrity during subsequent dives [2,4,5,7,9].

The Role of Oxidative Stress, Heat Shock Proteins, and Nitric Oxide

Oxidative stress is a principal mechanism underlying endothelial dysfunction following hyperbaric exposure. Increased oxygen partial pressure during diving enhances the production of reactive oxygen species (ROS), which reduce nitric oxide (NO) bioavailability, impair endothelial-dependent vasodilation, and activate inflammatory signaling pathways [2, 6]. Szyller et al. investigated the effects of simulated hyperbaric exposure on oxidative stress, heat shock proteins (HSPs), and nitric oxide synthase (NOS) responses in professional divers exposed to simulated dives at 30 m (400 kPa) and 60 m (700 kPa) for 24 h [4]. Superoxide dismutase (SOD) activity and malondialdehyde (MDA) concentrations significantly increased after both dive profiles. However, glutathione peroxidase (GPx) activity varied with diving depth, indicating that different hyperbaric conditions elicit distinct oxidative stress responses. [4]. Serum heat shock protein 70 (HSP70) concentrations decreased after both dive profiles, whereas heat shock protein 90 (HSP90) levels increased significantly following the 60-m exposure [4]. These findings suggest differential regulation of cellular stress-response pathways, with HSP70 primarily involved in cytoprotection and HSP90 participating in cellular signaling and adaptation to hyperbaric stress [4]. Furthermore, endothelial nitric oxide synthase (eNOS) concentrations increased after the 60-m dive, while inducible nitric oxide synthase (iNOS) remained unchanged [4]. The increase in eNOS may suggest a compensatory response to preserve endothelial function despite increased oxidative stress. Significant correlations between HSP expression and antioxidant enzyme activity further support the interaction between oxidative defense mechanisms and cellular stress-response pathways [4]. These findings align with previous studies

demonstrating that oxidative stress is a major contributor to endothelial injury after diving [3, 7]. They also support the concept that repeated hyperbaric exposure activates adaptive molecular pathways that may partially compensate for oxidative damage and preserve vascular homeostasis [5, 7]. Collectively, current evidence indicates that the balance between ROS generation, antioxidant capacity, HSP activation, and NO signaling is a key determinant of endothelial integrity during repeated diving exposure.

Inflammatory Status: Contrasting Findings in Recreational vs. Military Divers

Inflammatory activation is an important component of the vascular response to hyperbaric exposure. During decompression, venous gas emboli (VGEs) interact with the vascular endothelium, promoting platelet adhesion, complement activation, leukocyte recruitment, and microthrombus formation, all of which contribute to endothelial dysfunction and decompression-related vascular injury [2, 8]. Several studies have reported changes in circulating inflammatory and hematological markers, including leukocytes, platelets, and endothelial-derived microparticles, following diving exposure. However, the magnitude of these responses varies according to dive profile and diver characteristics [2, 3, 8].Acute recreational dives generally induce transient inflammatory activation with reversible endothelial impairment, whereas repeated occupational exposure may result in more complex physiological adaptations [3, 5]. Interestingly, available evidence suggests that inflammatory responses differ between recreational and professional divers. Moderate recreational SCUBA diving has been associated with transient activation followed by recovery of vascular homeostasis. However, military and commercial divers exposed to frequent hyperbaric hyperoxia may develop a persistent low-grade pro-inflammatory profile because of repeated oxidative and mechanical stress [2, 4, 7]. These findings indicate that the frequency, depth, breathing gas composition, and cumulative diving exposure are important determinants of vascular and inflammatory responses. Overall, the available evidence supports the concept that endothelial injury and inflammatory activation exist on a continuum ranging from transient physiological responses after occasional recreational diving to chronic vascular stress in individuals exposed to repeated occupational hyperbaric conditions Table 1. This variability may explain the apparently conflicting findings among previous studies and emphasizes the importance of cumulative exposure when evaluating long-term cardiovascular risk in divers [1, 3, 5, 7].

Table 1. Summary of Key Findings in Table Format

Study	Study Type	Population	Endothelial Function Measures	Key Findings
Madden et al. (2010)	Simulated	5 healthy divers	RH-PAT, CD105+ microparticles	Decreased endothelial function (RH-PAT index: -0.33 ± 0.27) after air diving; four-fold increase in CD105+ microparticles (from 440 ± 70 to 1306 ± 359) after air diving; no change after oxygen diving
Barak et al. (2020)	Field	11 breath-hold divers	FMD, total and subtype microparticles	Decreased FMD ($p < 0.001$); increased total microparticles ($p = 0.012$); 41% increase in CD31+/CD41- (endothelial-derived) and 60% increase in CD66b+ (neutrophil-derived) microparticles
Pontier et al. (2009)	Longitudinal	22 military divers	Skin blood flow (post-occlusive hyperemia and local heating), bubble grade (KISS)	No change in endothelial function; KISS bubble score decreased significantly from 16.4 ± 14.3 to 3.6 ± 9.2 after 90-day training; protective effect reversed 3 months

Study	Study Type	Population	Endothelial Function Measures	Key Findings
				after training cessation
Morabito et al. (2022)	Simulated	20 professional divers	SOD, GPx, MDA, HSP70, HSP90, eNOS, iNOS	Increased SOD activity and MDA concentrations after both dive profiles; decreased HSP70 after both dives; increased HSP90 after 60-meter dive; increased eNOS after 60-meter dive; significant correlations between HSP concentrations and SOD/GPx activities

Discussion

Summary of Main Findings

This review indicates that repeated hyperbaric exposure exerts both detrimental and adaptive effects on the vascular endothelium. Current evidence demonstrates that acute diving and decompression induce transient endothelial dysfunction through several interrelated mechanisms, including vascular gas bubble formation, oxidative stress, inflammatory activation, and endothelial microparticle (EMP) release [1–4,6–8]. Collectively, these mechanisms impair nitric oxide (NO) bioavailability, reduce endothelial-dependent vasodilation, and promote a pro-inflammatory and pro-thrombotic vascular environment. Numerous experimental studies have shown that decompression after compressed-air diving significantly impairs endothelial function and increases circulating endothelial microparticles (EMPs). This supports the idea that endothelial injury is one of the earliest biological responses to hyperbaric exposure [3, 8]. Besides, hyperoxic oxidative stress contributes to endothelial dysfunction through excessive reactive oxygen species (ROS) production and disruption of endothelial homeostasis [2, 4, 7]. Therefore, current evidence suggests that endothelial injury results from the combined effects of oxidative stress and bubble–endothelium interactions rather than from a single pathological mechanism.In contrast, studies on experienced military and professional divers indicate that repeated exposure may induce physiological adaptation. Pontier et al. noted that prolonged diving training significantly reduced post-dive vascular bubble formation without impairing baseline endothelial function, suggesting adaptive mechanisms that increase tolerance to hyperbaric stress [5]. These observations aligned with the endothelial dysfunction hypothesis proposed by Madden and Laden, which considers vascular gas bubbles as amplifiers rather than the sole initiators of decompression injury [6].Taken together, the available evidence supports a dynamic balance between endothelial injury and vascular adaptation. Acute dives are associated with transient endothelial dysfunction characterized by impaired vascular reactivity, oxidative stress, and inflammatory activation [1, 3, 4, 7, 8]. Conversely, repeated exposure may activate protective pathways involving antioxidant defenses, heat shock proteins (HSPs), and improved regulation of nitric oxide metabolism, thereby reducing susceptibility to decompression-related vascular injury [4,5,7]. Nevertheless, important knowledge gaps remain. Most available studies involve relatively small sample sizes and evaluate only short-term physiological responses after diving. Consequently, it remains unclear whether repeated hyperbaric exposure ultimately leads to cumulative endothelial injury or whether adaptive mechanisms provide sustained cardiovascular protection over years of professional diving. Well-designed longitudinal studies using standardized biomarkers of endothelial function are therefore required to clarify the long-term cardiovascular consequences of repetitive diving exposure.

Molecular Mechanisms Involved

Oxidative Stress: Oxidative Stress: Oxidative stress plays a crucial role in endothelial dysfunction following hyperbaric exposure. Hyperoxia increases reactive oxygen species (ROS), causing oxidative damage to proteins, lipids, and nucleic acids while reducing nitric oxide (NO) bioavailability and impairing endothelial-dependent vasodilation [2, 6]. Experimental evidence has demonstrated significant increases in superoxide dismutase (SOD) activity and

malondialdehyde (MDA) concentrations after simulated dives, confirming activation of oxidative stress pathways under hyperbaric conditions [4]. Recent evidence further suggests that the magnitude of oxidative stress depends on dive depth, oxygen partial pressure, and exposure duration, all of which influence endothelial recovery following repeated diving [7, 10]. Heat Shock Proteins (HSPs): Heat shock proteins play a crucial role in the body's adaptive response to hyperbaric stress. Szyller et al. reported a decrease in heat shock protein 70 (HSP70) along with an increase in heat shock protein 90 (HSP90) after deep simulated dives. This suggests a different regulation of cellular stress-response pathways under these conditions.HSP70 primarily exerts cytoprotective and anti-inflammatory effects, whereas HSP90 participates in intracellular signaling and vascular adaptation. These findings support the concept that repeated hyperbaric exposure activates endogenous protective mechanisms that may partially counteract endothelial injury [4, 7]. Nitric Oxide (NO) Signaling: Nitric oxide is essential for maintaining vascular homeostasis. It regulates several important functions, including vasodilation, platelet aggregation, leukocyte adhesion, and endothelial function. Hyperbaric exposure alters endothelial nitric oxide synthase (eNOS) activity, and increased eNOS expression after deep diving may represent a compensatory response to oxidative stress [4]. However, excessive ROS rapidly scavenges NO, limiting its biological activity despite increased enzyme expression [2, 7, 10]. Therefore, the balance between NO synthesis and oxidative degradation appears to be a critical determinant of endothelial function following repeated diving exposure. Endothelial Microparticles (EMPs): Endothelial microparticles have emerged as reliable biomarkers of endothelial injury induced by diving. Bubble–endothelium interactions stimulate EMP release, reflecting endothelial activation and apoptosis while promoting inflammation and coagulation [2, 8]. Clinical studies have consistently demonstrated increased circulating EMPs following both compressed-air and breath-hold diving, supporting their role as sensitive indicators of subclinical vascular injury [1, 3, 8]. Beyond their biomarker value, EMPs actively participate in intercellular communication by transferring inflammatory mediators and regulatory molecules, thereby amplifying endothelial dysfunction and contributing to persistent vascular injury after repeated hyperbaric exposure [7, 8].

Stress Response Versus Mechanical Injury

Evidence suggests that endothelial injury following diving results from both immediate mechanical effects and delayed biological responses. Madden et al. reported no significant changes in inflammatory biomarkers, including interleukin-6 (IL-6), E-selectin, P-selectin, or cortisol, during the early post-dive period despite clear evidence of endothelial dysfunction and increased endothelial microparticles (EMPs) [3]. These findings indicate that acute decompression injury is initially dominated by mechanical bubble–endothelium interactions rather than a systemic inflammatory response. In contrast, repeated hyperbaric exposure appears to activate delayed adaptive mechanisms involving antioxidant enzymes, heat shock proteins (HSPs), and endothelial protective pathways [4, 5, 7]. Therefore, the apparent discrepancy among previous studies is more likely explained by differences in biomarker assessment timing and cumulative diving exposure than by conflicting biological mechanisms. Acute mechanical injury and delayed cellular adaptation should be regarded as complementary rather than mutually exclusive processes [3–5, 7].

Individual Differences and the Role of Exercise

Individual susceptibility to endothelial dysfunction varies according to age, physical fitness, genetic background, hydration status, and cumulative diving exposure [2, 7]. Regular aerobic exercise improves endothelial function by increasing endothelial nitric oxide synthase (eNOS) activity, enhancing nitric oxide (NO) bioavailability, strengthening antioxidant defenses, and reducing vascular inflammation [2]. Consequently, good cardiovascular fitness may reduce vulnerability to diving-induced endothelial injury while facilitating recovery after repeated hyperbaric exposure. However, current evidence remains insufficient to establish the optimal intensity and timing of exercise before diving. Further prospective studies are needed to determine how exercise-based preconditioning influences endothelial adaptation and decompression-related vascular injury [2, 7].

Clinical Implications

The findings have several important implications for diving medicine and occupational health. First, transient endothelial dysfunction after diving suggests that adequate surface intervals may be necessary not only for inert gas elimination but also for vascular recovery, particularly following repetitive or deep dives [1, 3]. Second, evidence of physiological acclimatization indicates that progressive exposure to increasing dive depth and

frequency may enhance tolerance to hyperbaric stress while reducing post-dive bubble formation [5]. Furthermore, the balance between beneficial adaptation and cumulative vascular injury appears to depend on dive intensity, exposure frequency, and individual susceptibility [2, 4, 7]. These observations support regular cardiovascular risk assessment in professional divers and highlight the potential value of endothelial biomarkers, including endothelial microparticles (EMPs), for monitoring subclinical vascular injury [8]. Although antioxidant supplementation and other preventive strategies have been proposed, current clinical evidence remains insufficient to recommend their routine use [6, 7]. Future longitudinal studies are required to establish evidence-based recommendations regarding optimal dive scheduling, recovery intervals, exercise programs, nutritional interventions, and vascular monitoring in professional and recreational divers.

Limitations of Existing Studies and Knowledge Gaps

Despite considerable advances in understanding diving-induced endothelial dysfunction, several important limitations remain. First, the long-term cardiovascular effects of repeated hyperbaric exposure remain uncertain, as most available studies have short follow-up periods and relatively small sample sizes [2]. Consequently, it is unclear whether repeated subclinical endothelial injury contributes to premature vascular aging or cardiovascular disease. Moreover, the lack of diversity in participant characteristics, diving protocols, and assessment methods across published studies complicates generalizability. Most investigations have involved young, healthy military or professional divers, limiting the generalizability of findings to recreational divers, women, older individuals, and those with cardiovascular comorbidities [2, 7]. Additionally, endothelial function assessment using different techniques, including flow-mediated dilation (FMD), reactive hyperemia-peripheral arterial tonometry (RH-PAT), skin blood flow measurements, endothelial microparticles (EMPs), and circulating biomarkers, made direct comparison across studies difficult. Large prospective randomized studies were rare. Ethical and operational constraints make randomized diving trials challenging; therefore, current evidence relies predominantly on observational studies and experimental hyperbaric simulations [2, 7]. Furthermore, although molecular alterations involving oxidative stress, heat shock proteins (HSPs), nitric oxide (NO) signaling, and endothelial microparticles have been described, their precise interactions and long-term clinical significance in humans remain incompletely understood [4, 7, 8].Future investigations should adopt standardized endothelial assessment protocols, include larger and more diverse populations, and incorporate long-term follow-up to clarify the relationship between repeated hyperbaric exposure, endothelial adaptation, and cardiovascular outcomes.

Conclusion

Current evidence indicates that repeated hyperbaric exposure induces a dynamic balance between endothelial injury and vascular adaptation. Acute diving exposure is associated with transient endothelial dysfunction mediated by oxidative stress, bubble–endothelium interactions, and endothelial microparticle release [1, 4, 8]. In contrast, repeated diving may activate adaptive mechanisms that reduce post-dive bubble formation and enhance tolerance to hyperbaric stress without causing persistent endothelial dysfunction [4, 5]. The available data suggest that oxidative stress, nitric oxide signaling, heat shock proteins, and endothelial microparticles are key molecular pathways underlying these responses. However, whether repeated exposure ultimately promotes long-term vascular protection or cumulative endothelial injury remains uncertain because long-term prospective studies are scarce [2, 7]. Overall, endothelial dysfunction represents an important biological response to hyperbaric exposure and may serve as an early indicator of vascular stress in divers. Further well-designed longitudinal studies are required to define the long-term cardiovascular consequences of repeated diving and to establish evidence-based preventive strategies for professional and recreational divers**.**

Recommendations for Future Research

Future research should focus on large prospective longitudinal studies evaluating long-term cardiovascular outcomes in divers. Standardized assessment of endothelial function using flow-mediated dilation (FMD), endothelial microparticles (EMPs), and oxidative stress biomarkers would improve comparability among studies [1, 7, 8]. Additionally, mechanistic investigations should further clarify the roles of nitric oxide (NO), heat shock proteins (HSPs), oxidative stress pathways, and endothelial-derived microparticles in vascular adaptation to repeated hyperbaric exposure [4,7]. Finally, randomized clinical studies evaluating

preventive interventions, including exercise-based conditioning, nutritional strategies, and antioxidant approaches, are warranted before routine clinical recommendations [2, 6, 7].

Ethical Statements

This review article summarizes existing literature and does not involve any new experiments, human participants, animal studies, or the collection of personal data. Therefore, ethical approval was not required for this study.

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Authors' Contributions

Mohammad Moradi contributed to the conceptualization, literature review, writing, and revision of the manuscript. Hanieh Habibi Jirdehi provided assistance with the literature search and contributed to discussions related to the study. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this manuscript.

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