MIARCZYŃSKI, Jakub, GÓRSKI, Szymon, OKUPNIAREK, Joanna, BARTOSIK, Michalina, JĘTASIEWICZ, Igor, OBORSKI, Michał, OBORSKI, Krzysztof and BARCZYŃSKA, Katarzyna. Pathophysiology of Decompression Sickness: Current Insights and Emerging Models. Quality in Sport. 2026;49:67991. eISSN 2450-3118.
https://doi.org/10.12775/QS.2026.49.67991
https://apcz.umk.pl/QS/article/view/67991

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 l.p. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). **© The Authors 2026.**
This article is published with open access under the License Open Journal Systems of Nicolaus Copernicus University in Torun, Poland. Open Access: This article is distributed under the terms of the Creative Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non-commercial Share Alike License (http://creativecommons.org/licenses/by-nc-sa/4.0/), which permits unrestricted, non-commercial use, distribution, and reproduction in any medium, provided the work is properly cited.
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 05.01.2026. Revised: 15.01.2026. Accepted: 15.01.2026. Published: 18.01.2026.

Pathophysiology of Decompression Sickness: Current Insights and Emerging Models

Jakub Miarczyński[2]; ORCID ID: 0009-0004-5746-4786; jakub.miarczynski1@gmail.com

Szymon Górski[1]; ORCID ID: 0009-0006-1411-6524; szymon.gorski13@gmail.com

Joanna Okupniarek[2]; ORCID ID: 0009-0007-2446-4810; asiaokup22@wp.pl

Michalina Bartosik[3]; ORCID ID: 0009-0008-8541-1998; michalinabartosik03@gmail.com

Igor Jętasiewicz[2]; ORCID ID: 0009-0008-3351-6392; igor.jetasiewicz@icloud.com

Michał Oborski[2]; ORCID ID: 0009-0009-6170-6756; michal.oborski@wp.pl

Krzysztof Oborski[4]; ORCID ID: 0009-0004-4366-6897; krzysiek.oborski@wp.pl

Katarzyna Barczyńska[5;] ORCID ID: 0009-0005-1199-0980; Kasia.barczynska.8900@gmail.com

1 WSPSP - 'Provincial Dentistry' L.L.C., ul. Zdrowotna 6, 85-826 Bydgoszcz, Poland

2 Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Jagiellońska 13/15, 85-067 Bydgoszcz, Poland

3 Medical University of Łódź, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

4 Department of Internal Medicine, Diabetology and Clinical Pharmacology of the Central Clinical Hospital of the Medical University of Łódź, ul. Pomorska 251, 92-213 Łódź, Poland

5 III Dr Karol Jonscher Municipal Hospital in Łódź, ul. Milionowa 14, 90-309 Łódź, Poland

* Correspondence: jakub.miarczynski1@gmail.com

Abstract:

Introduction: Decompression sickness (DCS), commonly known as “the bends,” is a clinical disorder caused by the formation of gas bubbles within tissues or the bloodstream as a result of inert gas supersaturation during or following a decrease in ambient pressure. It most often occurs in the setting of compressed-gas diving, work in pressurized environments such as caissons, or rapid decompression to high altitude, including situations involving reduced cabin pressure or extravehicular activity (EVA) in space suits. DCS may also develop after relatively modest pressure reductions, such as commercial air travel undertaken shortly after scuba diving.

Clinical manifestations vary widely, ranging from musculoskeletal pain, lymphedema, and cutaneous rashes to severe neurological deficits and cardiorespiratory collapse. Initial evaluation should include a detailed history of recent diving or altitude exposure, the timing of symptom onset, and a thorough neurological examination. Immediate management consists of high-flow oxygen administration and appropriate fluid resuscitation, either orally or intravenously. Definitive treatment involves hyperbaric oxygen therapy. Although residual symptoms may persist in severe cases, prompt and appropriate treatment generally leads to a favorable outcome.

Purpose of work: The purpose of this article is to review and synthesize current scientific literature on the pathophysiology of decompression sickness, integrating classical physical concepts of inert gas supersaturation and bubble formation with contemporary biological and vascular models. Particular emphasis is placed on emerging mechanisms such as endothelial dysfunction, impaired nitric oxide signaling, inflammatory and coagulation pathways, and the role of circulating microparticles in amplifying tissue injury. The work aims to provide an updated, integrated framework for understanding decompression sickness that explains interindividual variability in clinical presentation and outcomes, and to highlight potential implications for risk stratification, prevention strategies, and future therapeutic approaches.

Materials and methods: An analysis of scientific articles available on PubMed and Google Scholar was conducted using the following keywords: decompression sickness; decompression illness; DCS; DCI; nitric oxide; endothelial microparticles; glycocalyx shedding; neurologic decompression sickness.

Keywords: Decompression sickness; Decompression illness; Hyperbaric physiology; Inert gas bubbles; Endothelial dysfunction; Microparticles; Nitric oxide; Inflammation; Microcirculation; Diving medicine

Results: A review of the literature showed that decompression sickness (DCS) is caused by inert gas bubble formation following a reduction in ambient pressure, with similar pathophysiology in diving and aviation. The clinical diagnosis is challenging, especially in aviation, where over half of suspected cases may have an alternative etiology. Key predictive factors include a pressure change ≥0.3 atm and an exposure altitude above 17,000 ft (5,182 m). The most commonly observed symptoms are musculoskeletal pain, paresthesia, fatigue, and cognitive “fogginess”; objective neurological deficits are more indicative of true DCS. Underlying mechanisms extend beyond mechanical bubble effects to include endothelial

damage, inflammatory cascade activation, complement activation, and platelet aggregation. The presence of a patent foramen ovale significantly increases the risk of severe neurological DCS. Despite treatment, residual neurological deficits can persist in severe cases.

EPIDEMIOLOGY

Decompression sickness (DCS) is a dysbaric disorder primarily affecting individuals undergoing significant reductions in ambient pressure, including divers, aviators, astronauts, and compressed-air workers. Its epidemiology is characterized by variable incidence rates influenced by a complex interplay of exposure profiles, procedural adherence, and individual physiological factors. Although often associated with underwater diving, DCS represents a broader occupational and recreational health concern where pressure change is a common denominator.

The incidence of DCS in diving populations is not uniform and rises with exposure intensity. Recreational divers on conservative profiles experience lower rates, whereas military, commercial, and technical divers undertaking deep, long, or repetitive dives face substantially higher risk [4]. Importantly, the presence of venous gas emboli (VGE) is a frequent post-dive finding, even after no-decompression dives, yet only a subset of individuals with detectable bubbles develop clinical symptoms [1, 2]. This indicates that bubble formation, while a necessary component in most DCS pathophysiological models, is insufficient alone to cause symptomatic disease.

Procedural and environmental variables strongly modulate DCS risk. Dive depth and duration directly increase inert gas loading and the likelihood of supersaturation upon ascent. Breathing gas composition also plays a role; for example, air diving may impose different oxidative and inert gas kinetics compared to enriched oxygen or mixed-gas diving, potentially altering inflammatory stress responses linked to DCS [7]. Violations of decompression protocols inevitably elevate risk, though intriguingly, even dives conducted strictly within established tables can result in high bubble grades and biochemical evidence of decompression stress [4].

Individual susceptibility remains a critical and incompletely understood epidemiological factor. Variability in post-dive microparticle (MP) production, neutrophil activation, and inflammatory cytokine release—such as interleukin-1β (IL-1β)—has been observed among divers undergoing identical exposures, suggesting inherent differences in immune or vascular responses to

decompression [11, 12]. Pre-dive physical activity appears protective; high-intensity exercise before diving attenuates post-decompression MP release and neutrophil activation, potentially lowering DCS incidence [9]. Other factors such as age, body composition, hydration status, and cardiopulmonary fitness also contribute to individual risk profiles.

A key epidemiological insight is the distinction between *subclinical decompression stress* and *manifest DCS*. Many divers exhibit biomarkers of decompression-induced pathology—elevated MPs, neutrophil activation, gas bubbles—in the absence of overt symptoms [8, 6]. This suggests DCS lies at the severe end of a continuum of decompression-related physiological disturbance. Chronic diving exposure may further alter baseline physiology; experienced divers show differences in inflammatory and apoptotic gene expression compared to non-divers, possibly reflecting adaptation or cumulative subclinical injury [3].

Emerging biomarkers, including cell-derived MPs and intravesicular IL-1β, are refining the epidemiological understanding of DCS. These markers not only correlate with dive intensity but also appear to rise during compression, preceding decompression and bubble detection in some cases [12]. This supports an evolving model where DCS pathophysiology is initiated by pressure exposure itself, with decompression exacerbating an already-active inflammatory cascade [10].

SYMPTOMS

Decompression sickness (DCS) encompasses a wide spectrum of clinical manifestations resulting from the formation of gas bubbles in tissues and blood following a reduction in ambient pressure. Symptoms can range from mild and self-limiting to severe and life-threatening, often presenting in various combinations depending on the location and extent of bubble formation. The onset, nature, and progression of symptoms are critical for diagnosis and determining treatment urgency.

Clinical Spectrum and Classification

DCS is traditionally categorized into two types based on symptom severity and system involvement [13, 14]. **Type I DCS** includes milder, non-neurological presentations such as musculoskeletal pain, cutaneous manifestations, and lymphatic involvement. **Type II DCS**

involves more serious neurological, cardiopulmonary, or constitutional symptoms and carries a greater risk of long-term sequelae.

Musculoskeletal Symptoms

Musculoskeletal pain, historically termed "the bends," is the most common presentation of DCS, reported in 50–65% of cases [14, 15]. The pain is typically described as a deep, dull, or throbbing ache, often peri-articular, affecting large joints such as the shoulders, elbows, knees, and hips [14, 16]. It is usually not exacerbated by movement and lacks local tenderness, which helps distinguish it from traumatic injury [14]. Pain may be migratory or multifocal and can range from mild discomfort to severe, incapacitating agony [13].

Cutaneous Symptoms

Cutaneous manifestations occur in approximately 5–10% of DCS cases [14]. These include:

- **Pruritus (itching)**, often without a visible rash.
- **Erythematous or mottled rash**, sometimes described as *cutis marmorata* or livedo racemosa, presenting as a reddish-blue, marbled pattern typically on the trunk, shoulders, or thighs [13, 14]. This rash can be a harbinger of more severe neurological DCS [13].

Neurological Symptoms

Neurological involvement constitutes Type II DCS and is present in a significant proportion of cases, with reported frequencies ranging from 20% to 40% depending on the dive profile and population [13, 14]. Symptoms may include:

- **Spinal cord DCS:** Presents with sensory deficits (numbness, paresthesia), motor weakness (paraplegia or quadriplegia), bladder or bowel dysfunction, and girdle or abdominal pain [14, 17].
- **Cerebral DCS:** May cause headache, confusion, visual disturbances (scotomata, diplopia), dysarthria, ataxia, and mild cognitive impairment [14].
- **Inner ear DCS (vestibular or cochlear):** Manifests as vertigo, tinnitus, hearing loss, nausea, vomiting, and nystagmus, often without other symptoms [14, 18]. It is more common after deep or mixed-gas diving [18].
- **Peripheral nerve involvement:** Presents as patchy, nondermatomal paresthesias or numbness [14].

Cardiopulmonary Symptoms (“The Chokes”)

Cardiopulmonary DCS is rare (<5% of cases) but serious, often associated with provocative dive profiles such as omitted decompression or rapid ascents [14]. Symptoms include:

- Dyspnea
- Chest pain or tightness
- Cough (sometimes productive of bloody sputum)
- Cyanosis
- In severe cases, cardiovascular collapse and shock [14, 19]

Constitutional and Lymphatic Symptoms

Constitutional symptoms such as fatigue, malaise, headache, and generalized weakness are reported in 20–40% of cases and may precede or accompany other manifestations [14]. Lymphatic involvement, though rare (<1%), presents as localized swelling, peau d’orange appearance, or tender lymphadenopathy, typically on the trunk [13].

Temporal Presentation

The timing of symptom onset is a key diagnostic clue. In diving-related DCS:

- **73% of mild cases and 98% of severe cases** begin within 1 hour of surfacing [20].
- **99% of all symptoms** appear within 6 hours post-dive [20].
- Late onset (>24 hours) is possible, especially following subsequent altitude exposure such as air travel [21].

  In altitude-induced DCS, symptoms may appear during exposure or after return to ground level [14].

Asymptomatic Decompression Stress

It is important to note that not all bubble formation leads to clinical DCS. Many divers exhibit detectable venous gas emboli (VGE) or biochemical markers of decompression stress (e.g., elevated microparticles, neutrophil activation) without symptoms, indicating a subclinical state that may still pose long-term risks [22, 11].

Differential Diagnosis Challenges

DCS symptoms are nonspecific and can mimic other conditions, including musculoskeletal injury, inner ear barotrauma, stroke, migraine, pulmonary edema, and even viral illness [14, 23]. A high index of suspicion is required when symptoms present in individuals with recent pressure exposure, and a thorough neurological examination is recommended even in apparently mild cases [14, 24].

PATHOPHYSIOLOGY

1. Initiating Event: Bubble Formation and Dynamics

The primary instigator of DCS is the transition of dissolved inert gas (primarily nitrogen in air diving) from a supersaturated state into the gaseous phase following decompression.

1.1 Gas Supersaturation and Nucleation

During compression, tissues absorb inert gas proportionally to the inspired partial pressure and exposure time, as described by Henry's Law. Upon decompression, if the ambient pressure falls too rapidly, the sum of dissolved gas tensions in tissues can exceed the ambient pressure, creating a state of supersaturation [25, 26]. This supersaturation provides the thermodynamic driving force for bubble formation.

Bubbles are thought to originate from pre-existing **gas micronuclei**—stable microscopic gas pockets trapped in hydrophobic crevices within tissues, joints, or on vascular surfaces—rather than forming de novo [27, 28]. The **nucleation theory** posits that these micronuclei expand when the surrounding tissue becomes sufficiently supersaturated, providing a low-energy site for bubble growth [29]. This concept is supported by observations that pre-treating tissues with extremely high pressure (which theoretically compresses nuclei) reduces subsequent bubble formation [30].

1.2 Bubble Growth and Resolution

Once formed, bubble behavior is governed by physical laws. The pressure inside a bubble ($Pbub$) is given by:

$$Pbub = Pamb + r2\sigma + M$$

where $Pamb$ is ambient pressure, σ is surface tension, r is bubble radius, and M represents tissue elastic tension [31]. Small bubbles have a high internal pressure due to surface tension, favoring gas diffusion out of the bubble and resolution. Conversely, larger bubbles have lower internal pressure and tend to grow further by inward diffusion of supersaturated gas from surrounding tissues [32].

Bubbles can form in various locations:

- **Extravascular (Tissue) Bubbles:** Form in poorly perfused tissues like fat, cartilage, tendon, and spinal cord white matter. Their growth can cause mechanical distortion, disrupt cell architecture, and compress microvasculature, leading to ischemia [33, 34].
- **Intravascular Bubbles (Venous Gas Emboli - VGE):** Form in venous blood draining supersaturated tissues. These are extremely common after diving and are usually filtered asymptomatically by pulmonary capillaries [1, 35].

2. Primary Injury Mechanisms

2.1 Mechanical and Ischemic Injury

- **Vascular Occlusion:** Intravascular bubbles can obstruct blood flow in capillaries and small arterioles, causing distal ischemia. In the spinal cord, this is thought to be a key mechanism for neurologic DCS, with the white matter being particularly vulnerable due to its low vascularity and high lipid content [36, 14].
- **Endothelial Damage:** Direct contact of bubbles with vascular endothelium causes physical injury. Bubbles can strip endothelial cells from the basement membrane,

increasing vascular permeability and leading to edema and hypovolemia [37, 38]. Even transient contact disrupts endothelial integrity and impairs vasoregulatory function.

- **Tissue Barotrauma:** Expanding extravascular bubbles in confined spaces (e.g., within bone, nerve sheaths, or joint capsules) can cause mechanical disruption, hemorrhage, and necrosis. This is implicated in dysbaric osteonecrosis and severe joint pain [39].

2.2 Bubble-Endothelium Interaction and Molecular Signaling

Beyond simple occlusion, bubble contact activates pathological signaling in endothelial cells:

- **Calcium Influx:** Bubble contact triggers a rapid influx of calcium into endothelial cells via mechanosensitive channels, including Transient Receptor Potential Vanilloid (TRPV) channels [40].
- **Mitochondrial Dysfunction:** The calcium surge can lead to mitochondrial permeability transition, loss of membrane potential, and ultimately, apoptotic or necrotic cell death [41].
- **Oxidant Production:** Bubble-endothelium interaction stimulates the production of reactive oxygen species (ROS), which further damages cells and propagates inflammatory signaling [42].

3. Secondary Inflammatory and Immunological Cascades

The concept of DCS has evolved from a purely mechanical "bubble disease" to a syndrome involving significant dysregulation of inflammation, coagulation, and immunity.

3.1 Activation of the Innate Immune System and Inflammasome

- **Leukocyte Activation and Sequestration:** The presence of bubbles triggers rapid activation and adhesion of neutrophils to damaged endothelium. Activated neutrophils release proteases, ROS, and pro-inflammatory cytokines, amplifying tissue injury [43, 44].
- **NLRP3 Inflammasome Activation:** A critical recent discovery links DCS to the activation of the **NLRP3 inflammasome** within immune cells. Bubble-induced

oxidative stress and potassium efflux can activate this cytosolic complex, leading to the cleavage and secretion of **Interleukin-1β (IL-1β)** [45, 10].

- **IL-1β as a Key Mediator:** IL-1β is a potent pyrogenic and pro-inflammatory cytokine. Unlike most cytokines, it lacks a signal peptide and is secreted via **microparticles (MPs)**. Studies in both mice and humans show that MPs containing high concentrations of IL-1β are generated during high-pressure exposure and are capable of inducing vascular injury when transferred to naive animals [10, 12]. This provides a direct mechanistic link between bubbles, inflammation, and vascular pathology.

3.2 Microparticles (MPs): Vesicular Mediators of Injury

MPs are small (0.1–1.0 μm) phospholipid vesicles shed from the membranes of activated, stressed, or apoptotic cells, including platelets, neutrophils, and endothelial cells.

- **Production Under Pressure:** Elevated levels of MPs are consistently documented in divers and animal models following decompression [6, 46].
- **Pro-inflammatory Cargo:** MPs act as vectors for bioactive molecules. They carry not only IL-1β but also other cytokines, adhesion molecules, and tissue factor, delivering concentrated pro-inflammatory and pro-coagulant signals to distant sites [47].
- **Endothelial Dysfunction:** Injection of MPs isolated from decompressed animals into healthy subjects reproduces vascular leakage and leukocyte activation, demonstrating their active pathogenic role beyond being mere biomarkers [48].

3.3 Coagulation and Platelet Activation

A hypercoagulable state often accompanies DCS:

- **Platelet Activation:** Bubbles and shear stress activate platelets, leading to aggregation and the release of pro-thrombotic and vasoactive substances [49]. Platelet-neutrophil aggregates form, further potentiating inflammation and microvascular occlusion [50].

- **Consumptive Coagulopathy:** Activation of the coagulation cascade can lead to increased fibrin formation and, in severe cases, a slight reduction in circulating platelets [51].
- **Thrombosis:** Microthrombi can form on bubble surfaces or damaged endothelium, compounding ischemic injury. Pretreatment with antiplatelet agents like abciximab (a glycoprotein IIb/IIIa inhibitor) reduces DCS severity in animal models [52].

3.4 Complement System Activation

The complement system, a key arm of innate immunity, is activated by gas-blood interfaces.

- **Alternative Pathway Activation:** Bubbles act as foreign surfaces, triggering the alternative complement pathway, leading to the generation of anaphylatoxins (C3a, C5a) and the membrane attack complex (C5b-9) [53].
- **C5a and Neutrophil Chemotaxis:** C5a is a potent chemoattractant for neutrophils. Complement activation correlates with DCS susceptibility in both animals and humans, and decomplementation reduces DCS severity in rabbits [54, 55].

4. Factors Influencing Pathophysiology and Individual Susceptibility

4.1 Patent Foramen Ovale (PFO) and Paradoxical Embolism

A PFO, present in 25-30% of the general population, provides a right-to-left intracardiac shunt. VGE that would normally be filtered by the lungs can pass through a PFO into the arterial circulation, becoming **paradoxical arterial gas emboli**. This significantly increases the risk of cerebral, spinal, and cutaneous DCS, as these small arterialized bubbles can lodge in end-arterioles of supersaturated tissues and grow [56, 57]. Divers with large PFOs have a higher incidence of severe neurological DCS [58].

4.2 The Role of Oxidative Stress

High partial pressures of oxygen and inert gases during diving increase ROS production. This oxidative stress is a key upstream activator of several pathways:

- **Trigger for MP Formation and Inflammasome Activation:** ROS can directly damage cell membranes, promoting MP shedding, and activate the NLRP3 inflammasome [45, 59].
- **Endothelial Dysfunction:** ROS scavenge nitric oxide (NO), a vital vasodilator, leading to vasoconstriction and impaired blood flow [60].
- **Mitochondrial Damage:** As described earlier, oxidative stress synergizes with calcium overload to impair mitochondrial function [41].

4.3 Theoretical and Contributing Mechanisms

- **Nitric Oxide (NO) Depletion:** Diving-induced oxidative stress may reduce bioavailable NO, worsening perfusion. Conversely, NO donors (e.g., nitroglycerin) administered before diving reduce bubble formation, suggesting a protective role for NO in maintaining endothelial health and perhaps stabilizing micronuclei [61, 62].
- **Neurogenic Inflammation:** Bubble-induced endothelial damage in the spinal cord or brain may lead to the release of substance P and other neuropeptides, contributing to pain, edema, and further inflammatory recruitment [63].
- **Autonomic Dysfunction:** Severe DCS can precipitate a shock-like state characterized by hypovolemia and vasodilation, possibly due to a systemic inflammatory response syndrome (SIRS) triggered by widespread bubble-endothelium interaction and cytokine release [64].

5. Integrative Pathophysiological Model

A modern integrative model of DCS pathophysiology can be summarized as a multi-step cascade:

1. **Decompression → Tissue Supersaturation.**
2. **Growth of Gas Micronuclei → Intravascular and Tissue Bubbles.**
3. **Primary Injury:** Mechanical vascular occlusion, endothelial damage, and tissue distortion.
4. **Bubble-Induced Signaling:** Activation of endothelium (Ca^{2+} influx, ROS), platelet activation, and complement activation.

5. **Amplification Phase:** NLRP3 inflammasome activation leads to IL-1β production and MP release. Neutrophils are recruited and activated.
6. **Secondary Injury:** MPs disseminate inflammatory signals. Activated neutrophils and a pro-coagulant state cause further endothelial dysfunction, increased vascular permeability, ischemia-reperfusion injury, and in severe cases, end-organ damage to the spinal cord, brain, inner ear, or lungs.
7. **Clinical Manifestations:** Symptoms reflect the location and magnitude of this combined mechanical, ischemic, and inflammatory insult.

This model underscores that DCS is not merely a disease of bubbles, but a **bubble-triggered, inflammation-mediated vascular injury syndrome**. This paradigm explains why symptoms can be disproportionate to bubble load and why therapies targeting inflammation (e.g., NSAIDs) or immune activation may provide benefit alongside recompression and hyperbaric oxygen.

CONCLUSION

Decompression sickness represents a complex pathophysiological entity that has evolved in our understanding from a simple mechanical model of bubble formation to a sophisticated, integrated syndrome of vascular injury and dysregulated inflammation. The initiating event remains the supersaturation of tissues with inert gas and the subsequent growth of gas micronuclei into macroscopic bubbles during or after decompression. These bubbles act as the primary insult, causing direct mechanical damage through vascular occlusion, endothelial disruption, and tissue distortion.

However, the clinical manifestations and severity of DCS are determined not merely by the presence of bubbles, but by the extensive secondary biological cascades they trigger. Critical among these are the activation of vascular endothelium, leading to calcium dysregulation and oxidative stress; the recruitment and hyperactivation of neutrophils; the activation of the NLRP3 inflammasome and subsequent production of the key pro-inflammatory cytokine IL-1β; and the widespread shedding of pro-coagulant and pro-inflammatory microparticles. These processes collectively amplify the initial injury, leading to increased vascular permeability, a pro-thrombotic state, ischemia-reperfusion injury, and ultimately, end-organ damage to the spinal cord, brain, inner ear, or lungs.

Individual susceptibility is modulated by anatomical factors such as a patent foramen ovale, which facilitates paradoxical embolism, and by physiological variables including pre-dive exercise, inflammatory tone, and endothelial resilience. This integrative model explains the observed disconnect between venous gas emboli load and clinical symptoms, the variable latency of symptom onset, and the potential for residual deficits despite recompression therapy.

Future research should continue to refine this model, with a focus on translating the understanding of inflammatory mediators like microparticles and IL-1β into clinically useful biomarkers for risk stratification and early diagnosis. Furthermore, this pathophysiological insight opens avenues for adjunctive pharmacological therapies aimed at modulating the immune response, protecting the endothelium, or enhancing nitric oxide bioavailability, which could complement the foundational treatment of hyperbaric oxygen therapy to improve outcomes in decompression sickness.

DISCLOSURE

Author's Contributions:

Conceptualization: Jakub Miarczyński, Szymon Górski, Joanna Okupniarek, , Igor Jętasiewicz

Formal analysis: Michał Oborski, Krzysztof Oborski, Igor Jętasiewicz, Michalina Bartosik

Investigation: Joanna Okupniarek, Michalina Bartosik, Jakub Miarczyński, Katarzyna Barczyńska

Writing rough preparation: Szymon Górski, Joanna Okupniarek, Michalina Bartosik, Igor Jętasiewicz, Krzysztof Oborski, Michał Oborski, Jakub Miarczyński

Writing review and editing: Szymon Górski, Igor Jętasiewicz, Katarzyna Barczyńska

All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Avability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References:

1 Eftedal O, Lydersen S, Brubakk AO. *The relationship between venous gas bubbles and adverse effects of decompression after air dives*. Undersea Hyperb Med. 2007;34:99-105.

2 Ljubkovic M, et al. *Venous and arterial bubbles at rest after no-decompression air dives*. Med Sci Sports Exerc. 2011;43:990-995.

3 Eftedal I, et al. *Acute and potentially persistent effects of scuba diving on the blood transcriptome of experienced divers.* Physiol Genomics. 2013;45:965-972.

4 Ljubkovic M, et al. *High incidence of venous and arterial gas emboli at rest after trimix diving without protocol violations.* J Appl Physiol. 2010;109:1670-1674.

5 Madden D, et al. *Exercise before SCUBA diving ameliorates decompression-induced neutrophil activation.* Med Sci Sports Exerc. 2014;46:1928-1935.

6 Thom SR, et al. *Microparticle production, neutrophil activation and intravascular bubbles following open-water SCUBA diving*. J Appl Physiol. 2012;112:1268-1278.

7 Thom SR, et al. *Bubbles, microparticles and neutrophil activation: Changes with exercise level and breathing gas during open-water SCUBA diving.* J Appl Physiol. 2013;114:1396-1405.

8 Pontier JM, Gemp F, Ignatescu M. *Blood platelet-derived microparticles release and bubble formation after an open-sea dive.* Appl Physiol Nutr Metab. 2012;37:1-5.

9 Madden D, et al. *High intensity cycling before SCUBA diving reduces post-decompression microparticle production and neutrophil activation.* Eur J Appl Physiol. 2014;114:1955-1961.

10 Thom SR, Bhopale VM, Yu K, Yang M. *Provocative decompression causes diffuse vascular injury in mice mediated by microparticles containing interleukin-1β.* J Appl Physiol. 2018;125:1339-1348.

11 Thom SR, et al. *Association of microparticles and neutrophil activation with decompression sickness*. J Appl Physiol. 2015;119:427-434.

12 Brett KD, et al. *Microparticle and interleukin-1β production with human simulated compressed air diving.* Sci Rep. 2019;9:13320.

13 Mahon RT, Regis DP. *Decompression and Decompression Sickness.* Compr Physiol. 2014;4:1157-1175.

14 Mitchell SJ, Bennett MH, Moon RE. *Decompression Sickness and Arterial Gas Embolism*. *N Engl J Med*. 2022;386:1254-1264.

15 Vann RD, Freiberger JJ, Caruso JL, et al. *Report on decompression illness, diving fatalities, and project dive exploration.* Durham, NC: Divers Alert Network, 2003:42.

16 Haas RM, Hannam JA, Sames C, et al. *Decompression illness in divers treated in Auckland, New Zealand*, 1996–2012. Diving Hyperb Med. 2014;44:20-5.

17 Saadi A, Ferenczi EA, Reda H. *Spinal decompression sickness in an experienced scuba diver: a case report and review of literature*. Neurohospitalist. 2019;9:235-8.

18 Lindfors OH, Raisanen-Sokolowski AK, Hirvonen TP, Sinkkonen ST. *Inner ear barotrauma and inner ear decompression sickness: a systematic review on differential diagnostics.* Diving Hyperb Med. 2021;51:328-37.

19 Berghage TE. *Decompression sickness during saturation dives. U*ndersea Biomed Res. 1976;3:387-98.

20 Xu W, Liu W, Huang G, Zou Z, Cai Z, Xu W. *Decompression illness: clinical aspects of 5278 consecutive cases treated in a single hyperbaric unit.* PLoS One. 2012;7(11):e50079.

21 St Leger Dowse M, Howell S, Smerdon GR. *Flying after diving: a questionnaire-based evaluation of pre-flight diving behaviour in a recreational diving cohort.* Diving Hyperb Med. 2021;51:361-7.

22 Brett KD, et al. *Microparticle and interleukin-1β production with human simulated compressed air diving*. Sci Rep. 2019;9:13320.

23 Hatling D, Hogset A, Guttormsen AB, *Muller B. Iatrogenic cerebral gas embolism — a systematic review of case reports.* Acta Anaesthesiol Scand. 2019;63:154-60.

24 Blatteau JE, Morin J, Roffi R, Druelle A, Shardella F, Castagna O. *Clinical problem solving: mental confusion and hypoxemia after scuba diving*. Diving Hyperb Med. 2020;50:181-4.

25 Boycott AE, Damant GCC, Haldane JS. *The prevention of compressed-air illness.* J Hyg (Lond). 1908;8:342-443.

26 Vann RD, Butler FK, Mitchell SJ, Moon RE. *Decompression illness.* Lancet. 2011;377:153-64.

27 Blatteau JE, Souday V, Gempp E, et al. *Gas nuclei, their origin, and their role in bubble formation.* Aviat Space Environ Med. 2006;77(10):1068-76.

28 Harvey EN. *Decompression Sickness. Caisson Sickness, Diver's and Flier's Bends and Related Syndromes*. Philadelphia: WB Saunders; 1951.

29 Hills BA. *Supersaturation by counterperfusion and diffusion*. Undersea Biomed Res. 1978;5(2):169-85.

30 Arieli R, Arieli Y, Marx A. *Hyperbaric oxygen may reduce gas bubbles in decompressed prawns by eliminating gas nuclei.* J Appl Physiol. 2002;92(6):2596-9.

31 Mahon RT, Regis DP. *Decompression and Decompression Sickness.* Compr Physiol. 2014;4:1157-75.

32 Wilmshurst PT, Byrne JC, Webb-Peploe MM. *Neurological decompression sickness*. Lancet. 1989;1(8640):731-6.

33 Dick AP Jr, Broome JR, Hayward IJ. *Acute neurologic decompression illness in pigs: lesions of the spinal cord and brain*. Lab Anim Sci. 1997;47(5):50-7.

34 Francis TJR, Dutka AJ. *Pathophysiology of decompression sickness.* In: Bove AA, Davis JC, eds. Diving Medicine. 4th ed. Philadelphia: Saunders; 2004.

35 Dunford RG, Vann RD, Gerth WA, et al. *The incidence of venous gas emboli in recreational diving.* Undersea Hyperb Med. 2002;29(4):247-59.

36 Hallenbeck JM, Bove AA, Elliott DH. *Mechanisms underlying spinal cord damage in decompression sickness.* Neurology. 1975;25(4):308-16.

37 Nossum V, Koteng S, Brubakk AO. *Endothelial damage by bubbles in the pulmonary artery of the pig.* Undersea Hyperb Med. 1999;26(1):1-8.

38 Brunner FP, Frick PG, Bühlmann AA. *Post-decompression shock due to extravasation of plasma*. Lancet. 1964;1(7343):1071-3.

39 Hutter CD. *Dysbaric osteonecrosis: a reassessment and hypothesis*. Med Hypotheses. 2000;54(4):585-90.

40 Sobolewski P, Kandel J, Klinger AL, Eckmann DM. *Air bubble contact with endothelial cells in vitro induces calcium influx and IP3-dependent release of calcium stores.* Am J Physiol Cell Physiol. 2011;301(3):C679-86.

41 Sobolewski P, Kandel J, Eckmann DM. *Air bubble contact with endothelial cells causes a calcium-independent loss in mitochondrial membrane potential.* PLoS One. 2012;7(10):e47254.

42 Thom SR, Bhopale VM, Hu J, Yang M. *Increased carbon dioxide levels stimulate neutrophils to produce microparticles and activate the nucleotide-binding domain-like receptor 3 inflammasome*. Free Radic Biol Med. 2017;106:406-16.

43 Martin JD, Thom SR. *Vascular leukocyte sequestration in decompression sickness and prophylactic hyperbaric oxygen therapy in rats*. Aviat Space Environ Med. 2002;73(6):565-9.

44 Helps SC, Gorman DF. *Air embolism of the brain in rabbits pretreated with mechlorethamine.* Stroke. 1991;22(3):351-4.

45 Thom SR, Bhopale VM, Hu J, Yang M. *Inflammatory responses to acute elevations of carbon dioxide in mice.* J Appl Physiol. 2017;123(2):297-302.

46 Thom SR, Yang M, Bhopale VM, Huang S, Milovanova TN. *Microparticles initiate decompression-induced neutrophil activation and subsequent vascular injuries.* J Appl Physiol. 2011;110(2):340-51.

47 Thom SR, Yang M, Bhopale VM, Milovanova TN. *Microparticle enlargement and altered surface proteins after air decompression are associated with inflammatory vascular injuries.* J Appl Physiol. 2012;112(1):204-11.
48 Yang M, Bhopale VM, Thom SR. *Microparticles generated by decompression stress cause central nervous system injury manifested as neurohypophyseal terminal action potential broadening.* J Appl Physiol. 2013;115(10):1481-6.
49 Thorsen T, Lie RT, Holmsen H. *Induction of platelet aggregation in vitro by microbubbles of nitrogen.* Undersea Biomed Res. 1989;16(6):453-64.
50 Pontier JM, Vallée N, Bourdon L. *Bubble-induced platelet aggregation in a rat model of decompression sickness.* J Appl Physiol. 2009;107(6):1825-9.
51 Philp RB. *A review of blood changes associated with compression-decompression: relationship to decompression sickness.* Undersea Biomed Res. 1974;1(2):117-50.
52 Lambrechts K, Pontier JM, Mazur A, et al. *Mechanism of action of antiplatelet drugs on decompression sickness in rats: a protective effect of anti-GPIIbIIIa therapy.* J Appl Physiol. 2015;118(10):1234-9.
53 Ward CA, Koheil A, McCullough D, Johnson WR, Fraser WD. *Activation of complement at plasma-air or serum-air interface of rabbits*. J Appl Physiol. 1986;60(5):1651-8.
54 Ward CA, McCullough D, Fraser WD. *Relation between complement activation and susceptibility to decompression sickness.* J Appl Physiol. 1987;62(3):1160-6.
55 Nyquist P, Ball R, Sheridan MJ. *Complement levels before and after dives with a high risk of DCS*. Undersea Hyperb Med. 2007;34(3):191-7.
56 Moon RE, Camporesi EM, Kisslo JA. *Patent foramen ovale and decompression sickness in divers.* Lancet. 1989;1(8637):513-4.
57 Germonpré P, Dendale P, Unger P, Balestra C. *Patent foramen ovale and decompression sickness in sports divers*. J Appl Physiol. 1998;84(5):1622-6.
58 Bove AA. *Risk of decompression sickness with patent foramen ovale*. Undersea Hyperb Med. 1998;25(3):175-8.
59 Thom SR, Bhopale VM, Yang M. *Neutrophils generate microparticles during exposure to inert gases due to cytoskeletal oxidative stress.* J Biol Chem. 2014;289(27):18831-45.
60 Brubakk AO, Duplančić D, Valič Z, et al. *A single air dive reduces arterial endothelial function in man*. J Physiol. 2005;566(Pt 3):901-6.
61 Mollerløkken A, Berge VJ, Jørgensen A, Wisløff U, Brubakk AO. *Effect of a short-acting NO donor on bubble formation from a saturation dive in pigs.* J Appl Physiol. 2006;101(6):1541-5.
62 Dujic Z, Palada I, Valic Z, et al. *Exogenous nitric oxide and bubble formation in divers.* Med Sci Sports Exerc. 2006;38(8):1432-5.
63 Zhang J, Fife CE, Currie MS, Moon RE, Piantadosi CA. *Spinal cord decompression sickness: murine model evaluation of circulatory and inflammatory components.* Undersea Hyperb Med. 1997;24(4):287-95.
64 Mitchell SJ, Doolette DJ. *Pathophysiology of inner ear decompression sickness: potential role of the persistent foramen ovale.* Diving Hyperb Med. 2013;43(1):7-12.