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Pathophysiology of Decompression illness and its effect on nervous system

Patofyziologie dekompresní nemoci a její účinky na nervový systém

Bachelor´s thesis

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Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Podpis

Abstract

Decompression sickness (DCS) is a diving-related condition caused by inert gas bubbles that form during or after a rapid reduction in ambient pressure. These gas bubbles can precipitate a cascade of mechanical vascular obstruction, ischemic injury, and inflammatory reactions, leading to a spectrum of clinical manifestations ranging from mild joint pain to severe neurological deficits. The nervous system is particularly vulnerable, with DCS affecting the brain, spinal cord, and inner ear in serious cases, often resulting in stroke-like symptoms, paralysis, or vertigo (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a).

This thesis summarizes the current state of knowledge on DCS pathophysiology and its neurological effects, incorporating evidence from both foundational research and recent studies. The formation of bubbles and subsequent biochemical responses, including activation of coagulation and inflammation, are examined as central mechanisms in DCS pathology. The role of D-dimer as a biomarker of coagulation activation in DCS is examined, highlighting studies that link elevated D-dimer levels with severe neurological outcomes (Emmanuel Gempp et al., 2012).

The impact of a patent foramen ovale (PFO) – a right-to-left cardiac shunt present in about a quarter of adults – on DCS risk and outcomes, as PFO allows venous bubbles to enter arterial circulation and has been associated with a higher incidence of neurological DCS (Germonpré et al., 2021). The long-term consequences of recurrent or severe DCS are explored, including persistent neurocognitive impairments and dysbaric osteonecrosis of bone (Sundal et al., 2022).

In addition, emerging research on the peripheral blood transcriptome and molecular mechanisms activated by decompression stress is analyzed. Gene expression analyses reveal an acute inflammatory and innate immune activation in divers with DCS, providing insight into the cellular pathways (e.g. neutrophil activation and cell adhesion molecule expression) that contribute to DCS pathology (Magri et al., 2021a).

DCS is a complex disorder with multifactorial injury mechanisms. Understanding its effects on the nervous system and identifying factors like coagulation markers, genetic expression changes, and anatomic risk factors (PFO) are crucial for improving diagnosis, treatment, and prevention strategies for divers and others at risk.

Key words: nervous system demage, decompression sickness, D-dimers, Patent foramen ovale, peripheral blood transcriptome, cell adhesion molecule (CAMs)

Abstrakt

Dekompresní nemoc (DCS) je potápěním vyvolaný stav způsobený bublinami inertního plynu, které vznikají během nebo po rychlém snížení okolního tlaku. Tyto plynové bubliny mohou spustit kaskádu mechanické cévní obstrukce, ischemického poškození a zánětlivých reakcí, což vede k širokému spektru klinických projevů od mírných bolestí kloubů po závažné neurologické deficity. Nervový systém je obzvláště zranitelný – v závažných případech DCS bývá zasažen mozek, mícha a vnitřní ucho, přičemž často dochází k příznakům podobným mozkové mrtvici, paralýze nebo vertigu (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a).

Tato práce shrnuje současný stav poznání patofyziologie DCS a jejích neurologických dopadů s využitím poznatků jak ze základního výzkumu, tak i z nejnovějších studií. Formování plynových bublin a následné biochemické odpovědi, zahrnující aktivaci koagulace a zánětu, jsou zde analyzovány jako ústřední mechanismy v patologii DCS. Zvláštní pozornost je věnována roli D-dimeru jako biomarkeru aktivace koagulace u DCS – studie ukazují, že zvýšené hladiny D-dimeru souvisí se závažnými neurologickými následky (Emmanuel Gempp et al., 2012).

Dále je popsán vliv otevřeného foramen ovale (PFO) – pravo-levého srdečního zkratu přítomného asi u čtvrtiny dospělých – na riziko a průběh DCS. Přítomnost PFO umožňuje průnik žilních bublin do arteriální cirkulace a byla spojena s vyšší incidencí neurologických forem DCS (Germonpré et al., 2021). Jsou také zkoumány dlouhodobé následky opakované nebo závažné DCS, včetně přetrvávajících neurokognitivních poruch a dysbarické osteonekrózy kostí (Sundal et al., 2022).

Kromě toho práce analyzuje nové výzkumné poznatky o periferním krevním transkriptomu a molekulárních mechanismech aktivovaných při dekompresním stresu. Analýzy genové exprese odhalují akutní zánětlivou a vrozenou imunitní odpověď u potápěčů s DCS a poskytují vhled do buněčných drah (např. aktivace neutrofilů a exprese molekul buněčné adheze), které přispívají k patologii DCS (Magri et al., 2021a).

DCS je komplexní poruchou s multifaktoriálními mechanismy poškození. Porozumění jejím účinkům na nervový systém a identifikace faktorů, jako jsou koagulační markery, změny genové exprese a anatomické rizikové faktory (PFO), je zásadní pro zlepšení diagnostiky, léčby a prevence u potápěčů i dalších rizikových skupin.

Klíčová slova: poškození nervového systému, dekompresní nemoc, D-dimery, Patent foramen ovale, transkriptom periferní krve, molekula buněčné adheze (CAMS)

List of Abbreviations

DCI	Decompression illness
AGE	Arterial Gas Embolism
CAMs	Cell Adhesion Molecules
CNS	Central Nervous System
DCI	Decompression Illness
DCS	Decompression Sickness
DWI	Diffusion Weighted Imaging
HBOT	Hyperbaric Oxygen Therapy
MRI	Magnetic Resonance Imaging
PFO	Patent Foramen Ovale
RLS	Right-to-Left Shunt
TCD	Transcranial Doppler
VGE	Venous Gas Embolism
T2WI	T2-Weighted Imaging

Contents

1. Introduction

Decompression sickness (DCS), commonly known as “the bends,” is a condition that arises from improper or rapid decompression after exposure to elevated ambient pressures, as encountered in scuba diving, hyperbaric chamber exposure, or high-altitude flight. It belongs to the broader category of decompression illness (DCI), which also encompasses arterial gas embolism. In DCS, inert gases, primarily nitrogen, absorbed in body tissues under high pressure form gas bubbles in blood and tissues upon too rapid return to lower pressure. These bubbles can provoke a complex pathophysiological response, including mechanical blockage of blood flow, direct tissue damage, and activation of inflammatory and coagulation pathways. (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a)

Clinically, DCS presentations are heterogeneous, ranging from mild Type I DCS to Type II DCS involving the nervous system with serious symptoms like motor weakness, sensory disturbances, vertigo, or loss of consciousness. Neurological involvement is particularly feared because it can lead to permanent disability. The brain, spinal cord, and inner ear are among the organs commonly affected in severe DCS, manifesting as stroke-like cerebral events, spinal cord syndromes - paraplegia or quadriplegia, and vestibular dysfunction. Such cases often occur within minutes to hours after surfacing and require urgent intervention. Hyperbaric oxygen therapy remains the cornerstone of DCS treatment, which can dramatically improve outcomes if applied early, especially for neurological DCS. (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a)

Despite decades of research and the development of dive tables and dive computers to minimize risk, our understanding of DCS pathophysiology is still evolving. Not all individuals or dives carry equal risk, and unexplained DCS can occur even when established decompression protocols are followed (Germonpré et al., 2021). This has prompted investigation into individual predisposing factors such as right-to-left shunts, biomarkers of decompression stress, and molecular changes that differentiate a safe dive from one leading to DCS (Dawn Kernagis, et al., 2015; Germonpré et al., 2021). In recent years, researchers have explored blood-based biomarkers like D-dimer and inflammatory mediators, as well as gene expression profiles, to better understand and predict DCS susceptibility and severity (Magri et al., 2021a). Parallel advances in imaging and neurophysiology have shed light on the lasting impact of DCS on the nervous system, even after acute symptoms resolve (Sundal et al., 2022).

This thesis provides a review of DCS with a focus on its neurological aspects. It will first outline the pathophysiology of decompression illness, describing how inert gas bubbles form and induce damage at the tissue and cellular levels. Next, it details the specific effects of DCS on the nervous system, covering the clinical manifestations and mechanisms of brain, spinal cord, and inner ear involvement. Then examines the role of D-dimers as biomarkers of DCS-related coagulopathy and their prognostic significance in neurological DCS. The influence of patent foramen ovale (PFO) on DCS risk and patient outcomes is reviewed, given its importance as a modifiable risk factor for arterial gas embolization. The thesis also discusses the long-term consequences of recurrent DCS, including chronic neurological sequelae and other organ damage from repeated bubble insults. Finally, it delves into the peripheral blood transcriptome and molecular mechanisms associated with DCS, highlighting research on genomic and molecular responses, such as inflammatory gene upregulation and cell adhesion molecule expression, that deepen the understanding of DCS at a systems

biology level. Through this multi-faceted exploration, the work aims to summarize current knowledge and identify gaps, with the goal of informing better preventive and therapeutic approaches for DCS in divers and other at-risk populations.

2. Clinical and Physical Foundations of Decompression Illness

Decompression illness (DCI) is caused by gas bubble formation in body tissues or the circulation as a result of a reduction in ambient pressure (Vann et al., 2011). Historically, the dangers of rapid decompression were first noted in 1670 by Robert Boyle, who observed a gas bubble in the eye of a snake and associated it with the creature's distress. In the 19th century, compressed-air workers (caisson laborers) frequently developed a mysterious paralytic condition termed "caisson disease," later understood to be decompression sickness. Pioneering work by Paul Bert in 1878 identified nitrogen gas uptake at high pressure and its sudden release as the cause of these symptoms. In 1908, John Scott Haldane developed the first decompression tables, introducing staged ascents to allow safe elimination of dissolved inert gas. Together, these foundational insights established that DCI arises from inert gas (primarily nitrogen) coming out of solution and forming bubbles during or after ascent, which can injure tissues and organs (Ninokawa and Nordham, 2022).

In modern usage, *DCI* is an umbrella term encompassing two related entities: decompression sickness (DCS) and arterial gas embolism (AGE) (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a). Both conditions share overlapping clinical features but have distinct pathophysiological mechanisms. DCI can occur not only in scuba divers but also in high-altitude aviators, astronauts, and others exposed to rapid decompression (Ninokawa and Nordham, 2022). The remainder of this chapter explores the clinical definitions and mechanisms of DCS and AGE, the physical gas laws underlying bubble formation, the physiological and molecular responses to bubbles (inflammation, coagulation, and related injury pathways), and the key environmental, physiological, and anatomical risk factors for DCI.

2.1 Decompression Sickness (DCS)

Decompression sickness (DCS) is a condition resulting from the formation of inert gas bubbles within body tissues and the bloodstream due to a rapid decrease in ambient pressure. During a dive, inert gases like nitrogen dissolve in body tissues in proportion to the surrounding pressure. If ascent occurs too quickly, these gases can come out of solution, forming bubbles that may cause mechanical obstruction of blood flow, direct tissue damage, and initiate inflammatory responses. (Chimiak J. et al., 2024)

Commonly affected areas include the musculoskeletal system and skin, leading to symptoms such as joint pain, muscle aches, and skin rashes within minutes to hours after surfacing. Historically, these milder manifestations were classified as Type I DCS, primarily involving the joints, skin, or lymphatic system (Cooper and Hanson, 2025). More severe cases, termed Type II DCS, affect the central nervous system—including the brain and spinal cord—or the cardiopulmonary system, presenting with neurological symptoms like limb weakness, paresthesias, ataxia, or pulmonary distress. Notably, neurological DCS often has an early onset, sometimes beginning within an hour of ascent, and can be life-threatening without prompt treatment. The Type I/II classification is considered imprecise by many experts, who now prefer to describe DCS based on the affected organ systems, acknowledging the spectrum of severity and symptom overlap. (Pollock N.W. et al., 2011)

Pathophysiologically, DCS bubbles can form in virtually any tissue. Bubbles within or adjacent to joints and tendons are believed to cause the deep, aching pain characteristic of the "bends." In the spinal cord or brain, bubbles can lead to localized ischemia or demyelination, resulting in neurological deficits such as paralysis or sensory impairments. Cutaneous manifestations like rashes or marbling, known as cutis marmorata, may occur due to vascular bubbles causing small-vessel occlusion. In severe cases, large volumes of intravascular bubbles can provoke hypotension and shock through combined cardiac outflow obstruction and systemic inflammatory effects. While mild cases of DCS may resolve over hours to days if untreated, serious cases carry a risk of permanent injury or death, underscoring the importance of prompt recognition and hyperbaric treatment. (Ninokawa and Nordham, 2022; Venkatesh et al., 2013)

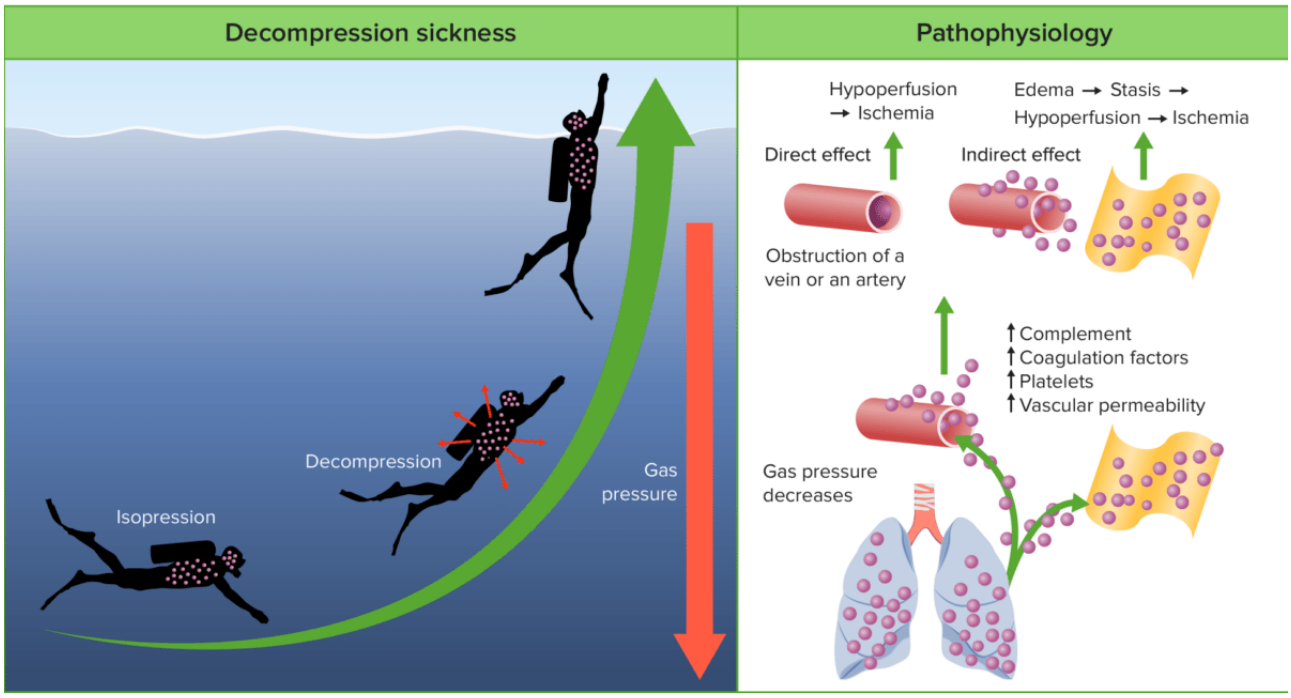

Figure 1. Pathophysiology of Decompression Sickness: During descent under increased ambient pressure, inert gases dissolve into the body's tissues and bloodstream in accordance with Henry's law. Upon ascent and decompression, the reduction in ambient pressure leads to tissue supersaturation, promoting the liberation of dissolved gases as free bubbles. Small quantities of these bubbles are typically filtered by the pulmonary capillary network without clinical consequence. However, when bubble formation is extensive, they can provoke direct vascular obstruction, initiate platelet aggregation and activation of the coagulation cascade, induce capillary endothelial damage and leakage, and trigger a systemic inflammatory response, collectively contributing to the pathogenesis of decompression sickness. Image by Lecturio, 2025.

2.2 Arterial Gas Embolism (AGE)

Arterial gas embolism is a distinct form of DCI that occurs when expanding gas in the lungs escapes into the arterial circulation, producing large bubbles that travel to end organs. In divers, AGE most often results from pulmonary barotrauma: if a diver holds their breath during ascent or has trapped air in the lungs (due to lung disease or a rapid uncontrolled ascent), the decreasing pressure can cause the alveoli to rupture (in accordance with Boyle's law; see below). This allows air to pass into the pulmonary veins and left side of the heart, distributing arterial bubbles systemically. Even a small volume of arterial gas can occlude the blood supply of critical organs. The brain is the principal target organ in AGE, as its blood flow may be blocked by the emboli, leading to cerebral ischemia. Clinically, AGE typically presents immediately upon surfacing or within minutes, often with sudden loss of consciousness, stroke-like symptoms, confusion, or seizures. Cardiovascular collapse can occur if the embolus "air-locks" the heart or major vessels. In some cases, divers will surface unconscious or experience convulsions almost instantly, which is a classic presentation of acute cerebral arterial gas embolism. (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a).

Because AGE results from a physical lung over-pressure injury, it can occur even in relatively shallow dives if a diver panics or ascends without exhaling. Importantly, the distinction between AGE and DCS can be challenging in practice, since both may cause neurological symptoms. Classically, AGE has an abrupt onset (within moments of surfacing), whereas DCS neurological symptoms, from spinal cord or cerebral involvement, might begin a bit later (tens of minutes to hours post-dive). However, overlap exists for example, a diver who surfaces unconscious could have either an arterial embolism or massive DCS affecting the brain. For this reason, the term *decompression illness (DCI)* is used to encompass both AGE and DCS without needing to immediately differentiate their origin (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a). In a diving casualty, any signs of stroke, paralysis, or altered consciousness after ascent are treated presumptively as DCI, and management (recompression therapy) addresses both possibilities. Differentiating the two entities is less important clinically than initiating prompt treatment. That said, understanding the pathophysiological differences is crucial: DCS arises from dissolved inert gas coming out of solution, whereas AGE is fundamentally a barotrauma-induced embolic event. The following sections review the physical laws that govern these processes and the biological impacts of intravascular versus extravascular bubbles.

2.3. Physical Gas Laws Relevant to Decompression

The behaviour of gases under pressure follows well-defined physical laws that underpin the physiology of diving and the pathogenesis of DCI. Three primary gas laws are particularly relevant:

Boyle's Law

Boyle's law states that at constant temperature, the volume of a gas is inversely proportional to the ambient pressure. In mathematical form:

Equation 1: Boyle's Law

$$P_1V_1 = P_2V_2$$

where:

- P_1= initial pressure
- V_1 = initial volume
- P_2 = final pressure
- V_2 = final volume

In practical terms, if the surrounding pressure is halved, a gas will double in volume. For divers, Boyle's law explains why gas in the lungs or other body air spaces expands during ascent as pressure decreases. For example, a breath of air taken at 30 meters depth (approximately 4 atmospheres absolute pressure) will expand to about four times its volume at the surface. This expansion is normally vented harmlessly by exhalation. However, if a diver holds their breath or has air trapped, as in a blocked airway or lung disease, the expanding gas can rupture lung tissue (pulmonary barotrauma), potentially releasing air bubbles into the bloodstream. The precipitating event for AGE Boyle's law also underlies the concept of *squeeze* and *expansion* in other air spaces (such as sinuses or mask), and conversely, it is the principle by which therapeutic recompression shrinks bubble volume to help resolve DCI. (Jones et al., 2025)

Henry's Law (Gas Dissolution)

Henry's law states that at a constant temperature, the amount of gas dissolved in a liquid is directly proportional to the partial pressure of that gas in contact with the liquid. In diving physiology, this means that when a diver is at depth breathing compressed air, the high ambient pressure causes more nitrogen to dissolve in the blood and tissues than at the surface. Tissues take up inert gas until they reach equilibrium with the inspired gas at that pressure. The longer and deeper the dive, the more nitrogen is absorbed by the body's tissues. When the diver ascends, the ambient pressure and thus the partial pressure of dissolved nitrogen drops. If the pressure reduction is too rapid, the dissolved gas becomes supersaturated relative to the new ambient pressure and can come out of solution as bubbles. Henry's law thus explains the fundamental cause of DCS: inert gas uptake under high pressure and bubble liberation upon decompression. Controlled, slow ascents and staged decompression stops mitigate DCS risk by giving the body time to eliminate excess dissolved gas via the lungs before bubbles form. (Chandan and Cascella, 2025)

Dalton's Law (Partial Pressures)

Dalton's law of partial pressures states that the total pressure of a gas mixture is the sum of the partial pressures of each constituent gas. Each gas in a mixture exerts a pressure proportional to its fraction of the mixture. At sea level (1 atm), for example, oxygen at ~21% of air has a partial pressure of ~0.21 atm, and nitrogen at ~78% has ~0.78 atm. In diving, although the gas fractions in a tank might be the same as at the surface (for air, 21% O_2, 78% N_2), the partial pressure of each gas increases in direct proportion to the ambient pressure. At 30 m depth (4 atm total pressure), the partial pressure of nitrogen in air is about 3.12 atm (4 × 0.78). According to Dalton's law, this elevated nitrogen partial pressure is what drives more nitrogen into the diver's tissues (per Henry's law). Dalton's law also underlies why breathing gas mixtures can be adjusted for deep dives (for instance, replacing some nitrogen with helium in trimix to reduce nitrogen partial pressure and narcosis at depth). In the context of DCI, Dalton's law simply emphasizes that the physiological impact of a gas (inert gas uptake, oxygen toxicity, etc.) is governed by its partial **pressure**, which increases with depth. Thus, understanding partial pressures is key to grasping why deeper or longer exposures lead to more inert gas loading and greater decompression stress. (Jones et al., 2025).

2.4 Inert Gas Uptake and Bubble Formation During Ascent

When a diver descends and remains under increased pressure, inert gas dissolves into the body's fluids and tissues. Different tissues take up gas at different rates depending on their perfusion and solubility characteristics – a concept formalized in classical decompression models by Haldane and Boycott (Boycott et al., 1908). Tissues like blood and brain, which have high blood flow, equilibrate with ambient pressure relatively quickly, whereas adipose tissue and cartilage absorb gas more slowly but can ultimately hold larger quantities, due to higher lipid solubility of nitrogen. With prolonged time at depth, tissues approach saturation with the inert gas at the prevailing pressure. As long as the diver remains under pressure, the inert gas remains dissolved harmlessly. The *ascent* phase is critical: if ambient pressure is reduced gradually, the excess gas can diffuse back into the blood and be exhaled through the lungs. However, if decompression is too rapid, tissues become supersaturated with gas, meaning the partial pressure of dissolved gas exceeds what can stay in solution at the lower pressure. Supersaturation creates the conditions for bubble formation (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a; Ninokawa and Nordham, 2022)

Bubble formation in the body does not necessarily happen spontaneously at the exact moment of supersaturation; it often requires initiation at gas nuclei or interfaces. It is believed that microscopic gas pockets (so-called *pre-existing nuclei* or micron-sized bubbles) in tissues and blood serve as seeds for bubble growth when supersaturation occurs. These gas nuclei can originate from normal physiological processes and usually remain undetectably small at higher pressures. Upon ascent, as the pressure falls, those nuclei can expand. Additionally, movement or mechanical forces might promote bubble coalescence, a process sometimes termed *tribonucleation*. Once a bubble is formed, it will grow if the surrounding tissue gas tension is higher than ambient, driving more gas out of solution into the bubble. Bubbles may initially form within tissues (extravascular bubbles) or inside the vasculature (venous gas emboli, VGE).

Small venous bubbles are commonly detected in divers after ordinary dives using Doppler or ultrasound, even if no DCS symptoms develop. In fact, many divers can have asymptomatic VGE, which are normally filtered out by the pulmonary circulation without issue. Problems arise when the quantity or size of bubbles is sufficient to overwhelm the lung's filtration capacity, or when bubbles form in or migrate to sensitive locations. If venous bubbles pass through the lung into the arterial circulation - for example, via a heart defect like a patent foramen ovale, they can cause arterial embolisms similar to AGE. Bubbles that remain within tissues can compress blood vessels or nerves locally. The likelihood of bubble formation and growth is influenced by the degree of supersaturation (which depends on dive depth, duration, and ascent rate) and individual factors such as tissue properties. Modern decompression tables and dive computer algorithms are designed to limit supersaturation in any "compartment" to reduce bubble risk, but they cannot eliminate it entirely. Thus, an ascent that is too fast or exceeds decompression limits may result in bubbles forming faster than they can be eliminated, leading to DCS. (Naval Sea Systems Command, 2018)

2.5 Biological Responses to Gas Bubbles

Gas bubbles formed during decompression can cause harm through multiple mechanisms. These bubbles are categorized as intravascular (circulating within blood vessels) or extravascular (lodged within tissues). Both types can induce direct mechanical effects and initiate complex biochemical responses (Vann et al., 2011).

2.5.1 Intravascular Bubbles: Inflammation and Coagulation

Intravascular bubbles can act as emboli, physically obstructing small vessels and reducing blood flow to distal tissues, leading to ischemia (Brubakk et al., 2007). Beyond mechanical blockage, these bubbles provoke inflammatory and thrombotic responses (Thom et al., 2015). Studies have shown that bubbles can activate blood components and the endothelium: platelets adhere to bubble surfaces and become activated, initiating coagulation; the contact of gas with blood can trigger the complement system and kinin cascades, leading to the release of inflammatory mediators (Brubakk et al., 2007; Thom et al., 2015). Endothelial cells lining the vessels can be damaged by the shear stress of bubbles or by nitrogen gas coming out of solution within the endothelium, causing these cells to express adhesion molecules and promote leukocyte activation (Brubakk et al., 2007). Neutrophils and other leukocytes aggregate at bubble sites and release inflammatory cytokines and free radicals, contributing to local tissue injury and capillary leak (Brubakk et al., 2007; Vann et al., 2011).

A notable consequence of intravascular bubbles is the generation of microparticles—submicron vesicles shed from blood and endothelial cells. Elevated levels of circulating pro-inflammatory microparticles have been observed in divers with decompression sickness (Thom et al., 2015). These microparticles, likely produced when bubbles exert stress on cell membranes, can further propagate inflammation and coagulation. Thom et al. demonstrated an association between elevated microparticles, neutrophil activation, and DCS in divers (Thom et al., 2015). The cumulative effect of these processes can lead to intravascular injury: clots may form ranging from microthrombi to, in severe cases, disseminated intravascular coagulation, and blood flow can be compromised in various organs beyond the initial bubble occlusion (Brubakk et al., 2007; Vann et al.,

2011). In extreme scenarios, this manifests as hypovolemic shock and massive coagulopathy, although such outcomes are rare (Vann et al., 2011). More commonly, the inflammatory response contributes to symptoms like malaise and fatigue seen in DCS, and coagulation at bubble sites may play a role in specific injuries, such as spinal cord infarction due to bubbles in the epidural venous plexus causing clotting and venous outflow obstruction (Moon et al., 1989; Vann et al., 2011).

It is important to note that the presence of circulating bubbles does not always correlate with clinical DCS: many divers exhibit high grades of venous bubbles post-dive without symptoms. This suggests that individual susceptibility—possibly due to genetic differences in inflammatory and coagulation responses—modulates the outcome. Animal studies have shown strain differences in DCS susceptibility, and researchers have bred rodents for DCS resistance, finding that resistant phenotypes have differing hematologic and vascular response profiles. Thus, while intravascular bubbles initiate a cascade of events, the progression to clinical illness depends on complex interactions between the bubbles and the host's response (Thom et al., 2012; Vann et al., 2011).

2.5.2 Extravascular Bubbles: Tissue Injury and Local Effects

Bubbles that form within tissues cause damage largely by their mechanical presence and expansion in confined spaces. For example, an extravascular nitrogen bubble in peri-articular tissues can stretch joint capsules or tendons, generating the pain of the musculoskeletal "bends." In the spinal cord or brain, bubbles in the white matter or other parenchymal locations can compress or shear delicate structures, leading to neurological deficits. Haldane's early microscopic examinations revealed nitrogen bubbles in spinal cord white matter of animals, highlighting direct tissue invasion by bubbles as a mechanism of injury (Ninokawa and Nordham, 2022). Extravascular bubbles may also compress local blood vessels from outside, causing ischemia of tissues. For instance, a bubble in the spinal epidural space or embedded in tissue could press on spinal veins or arterioles, compounding the damage by reducing perfusion to the spinal cord. The term "autochthonous bubbles" has been used for bubbles forming locally within tissues (as opposed to intravascular emboli), and these are thought to be a primary cause of certain DCS manifestations such as spinal cord lesions. (Naval Sea Systems Command, 2018)

In addition to direct mechanical harm, extravascular bubbles provoke local inflammatory responses. Tissue-resident cells (e.g. macrophages, mast cells, endothelial cells) sense the presence of a bubble and can become activated, releasing inflammatory mediators that cause edema and pain. For example, bubbles in muscle or skin incite histamine release and cytokine production, which contribute to the characteristic swelling and rash in cutaneous DCS (skin bends). In the inner ear, bubble formation in the fluid spaces or vasculature can trigger a severe vestibular injury with vertigo and hearing loss; this has been linked not only to mechanical blockage but also to secondary inflammation in the delicate inner ear structures. The body's attempts to reabsorb or wall off extravascular bubbles can further induce a localized immune response.

Both intravascular and extravascular bubbles ultimately lead to cell dysfunction or death in affected areas. The clinical manifestations of DCI are the net result of these direct and indirect effects. The recognition that inert gas bubbles initiate multi-system injury pathways – mechanical, ischemic, inflammatory, and pro-

thrombotic – helps explain why pure recompression, which addresses only the mechanical aspect by shrinking bubbles, may not immediately reverse all symptoms. Adjunct therapies like fluids, oxygen, anti-inflammatories often aim to mitigate the secondary injury processes initiated by bubbles.

3. Neurological and neurophysiological impact of Decompression illness.

The nervous system is highly vulnerable to decompression sickness, and neurologic involvement is common in serious cases. In dive accidents with severe DCS, one or more major symptoms are frequently neurologic in origin. In fact, the central nervous system – particularly the spinal cord, brain, and vestibular structures – is often affected by inert gas bubble formation during rapid decompression (Newton M.D. et al., 2001). Among these, the spinal cord appears especially at risk. Clinical data indicate the spinal cord is the most commonly affected site in neurological DCS, with the thoracic cord being particularly susceptible (Saadi et al., 2019). This vulnerability is thought to derive from the cord's unique anatomy: the spinal cord's white matter absorbs and dissolves large amounts of nitrogen under pressure, and its blood flow is relatively low, leading to slower nitrogen washout. These factors create a scenario where bubbles readily form and persist in spinal cord tissue during decompression, making the cord prone to ischemic injury. Correspondingly, post-mortem and imaging studies of divers with neurological DCS often show lesions in the spinal white matter (especially dorsal columns) and brain white matter, reflecting high nitrogen solubility in myelin-rich areas (Kamtchum Tatuene et al., 2014).

3.1 Cerebral DCS

Cerebral decompression sickness is a relatively uncommon manifestation of decompression illness but constitutes a significant subset of neurological DCS cases. The overall incidence of all forms of DCS in recreational diving is approximately 1 case per 10,000 dives (Mitchell et al., 2022). However, this risk substantially increases with extreme exposures. Technical divers reported approximately 91 cases per 10,000 dives (0.91%) when including mild, self-treated symptoms (Tuominen et al., 2022). Among DCS cases, spinal and cerebral DCS is frequently observed. In particular, cerebral DCS may account for a substantial proportion of serious DCS cases. A retrospective 20-year series from Belgian hyperbaric centres documented 286 cerebral DCS cases out of 595 total DCS cases, accounting for about 48% of severe cases (Lafère et al., 2017).

The clinical spectrum of cerebral DCS ranges from subtle cognitive alterations to severe stroke-like deficits. Symptoms typically present within minutes to hours after surfacing; over half appear within the first hour, and approximately 90% within 6 hours (Cooper and Hanson, 2025). Common clinical features include alterations in mental status such as confusion, slowed cognition, and dysexecutive symptoms affecting concentration and decision-making. Unusual fatigue, personality changes, headache, visual disturbances, dysarthria, limb weakness, numbness, gait instability, and coordination issues are also frequently reported (Cooper and Hanson, 2025; School of Medicine, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand et al., 2018). These manifestations are generally less dramatic compared to arterial gas embolism (AGE), which often involves immediate dense hemiplegia or loss of consciousness (Moon, Richard E., 2023). Cerebral DCS symptoms commonly develop more gradually compared to AGE, emerging after a latent period rather than immediately upon surfacing. Both conditions, however, require similar urgent recompression treatment (Cooper and Hanson, 2025; Moon, Richard E., 2023).

The critical factor for cerebral DCS is arterial bubble embolization, typically via right-to-left cardiac or intrapulmonary shunts such as a patent foramen ovale (PFO), present in 25–30% of adults (Hexdall and

Cooper, 2025). Bubbles lodged in cerebral vessels obstruct blood flow, damage endothelium, disrupt the blood-brain barrier, and trigger inflammatory and coagulation cascades (Blogg et al., 2014). High loads of microscopic bubbles can transiently impair cerebrovascular reactivity, causing diffuse neurological symptoms (Blogg et al., 2014; Edvinsson et al., 2021). A single large gas embolus can occlude major cerebral arteries, causing stroke-like symptoms. Cerebral DCS and AGE thus represent a spectrum of arterial gas injuries distinguished primarily by onset timing and specific mechanisms (Blogg et al., 2014).

Anatomically, a significant risk factor is the presence of a PFO, which dramatically increases neurological DCS risk. A cohort study found 64% of divers with initial cerebral DCS episodes had a PFO compared to about 25% prevalence in the general population, and recurrent episodes correlated with larger shunt sizes (Lafère et al., 2017).

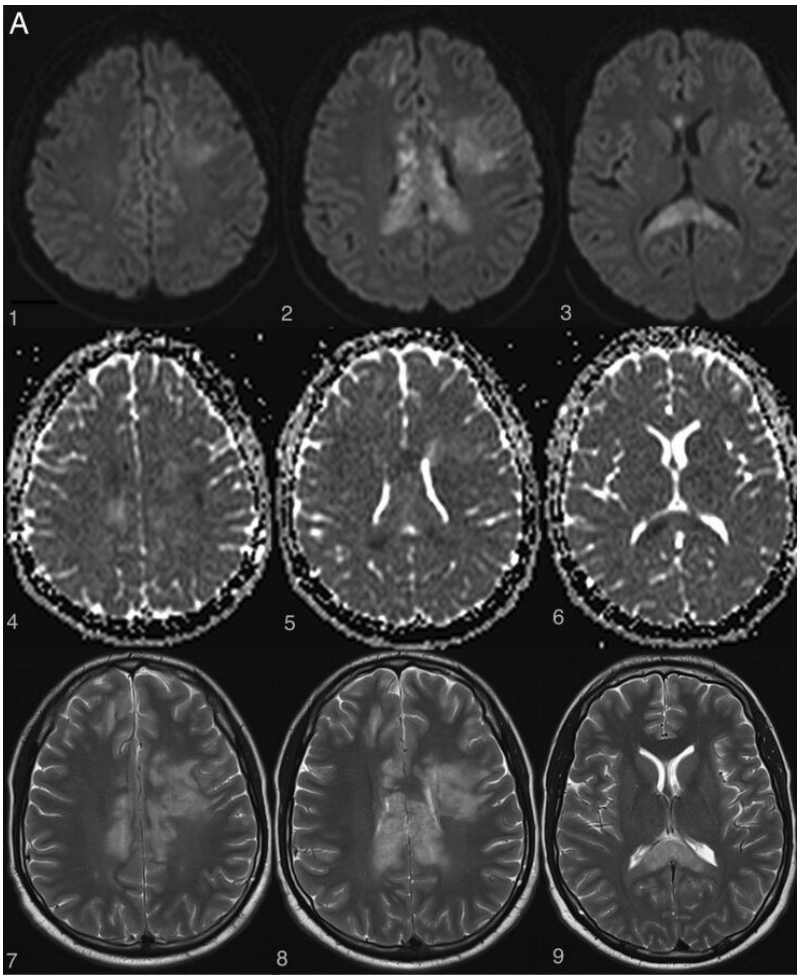

Figure 2. Illustrative cases of permanent brain damage caused by decompression sickness in a single patient. On diffusion-weighted imaging, restricted diffusion areas match lesions found in the corpus callosum and bilateral frontal white matter. These lesions are also identified as hyperintensities on T2-weighted imaging, resembling characteristics typically observed in ischemic or necrotic central nervous system injuries. Picture from Tatuene et al.

Neuroimaging, though not always routinely performed, helps evaluate cerebral involvement in DCS. MRI can show ischemic lesions correlating to bubble-induced injuries, particularly with severe presentations. Diffusion-weighted imaging (DWI) often identifies acute ischemic lesions similar to embolic strokes. Mild or transient symptoms may yield normal or subtle MRI findings. Chronic changes such as T2-weighted hyperintensities in white matter have also been documented, though their direct relation to diving remains uncertain (Coco et al., 2019). Transcranial Doppler ultrasound with bubble contrast can detect right-to-left shunts and confirm the suspected mechanism of cerebral DCS (Grosset et al., 1996).

Prognosis significantly depends on the severity of the initial injury and the promptness of treatment. Hyperbaric oxygen therapy is the primary treatment and generally leads to good recovery outcomes if administered early. About 80% of neurological DCS patients experience no or minimal residual symptoms following timely treatment (Mitchell et al., 2022). Severe cases, delayed treatments, or recurrent episodes can result in permanent deficits, including chronic weakness, cognitive impairment, or gait disturbances. Recurrent cerebral DCS typically leads to worse outcomes, emphasizing preventive measures such as conservative dive profiles or PFO closure (Lafère et al., 2017; Sundal et al., 2022).

3.2 Spinal Cord DCS

The spinal cord is a major target organ in decompression illness. Epidemiological reports and case series indicate that spinal cord DCS constitutes a large proportion of all neurological DCS cases (Kamtchum Tatuene et al., 2014; Saadi et al., 2019). In one review of DCS cases, spinal cord lesions represented the majority of CNS injuries in Type II Neurologic DCS (Kamtchum Tatuene et al., 2014). Clinically, spinal DCS often manifests as an acute myelopathy with sensorimotor deficits in the lower trunk and limbs. Motor weakness is very common – studies report paraplegia or paraparesis in about 20–25% of neurologic DCS cases – and sensory disturbances, paresthesia or anesthesia, occur in approximately 20–30% cases. In many patients, both motor and sensory symptoms coexist, reflecting combined dorsal and lateral column involvement. The thoracic cord is most frequently affected, followed by the cervical region, lumbar involvement is less common (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024b; Kamtchum Tatuene et al., 2014).

The predilection for the thoracic spinal cord in DCS is attributed to its anatomy and perfusion. The dorsal and lateral columns of the cord have a high myelin-rich lipid content, allowing them to absorb more nitrogen during a dive. At the same time, the blood supply and venous drainage of the thoracic cord is relatively slow, especially in the watershed areas of the anterior spinal artery. Upon ascent, these regions can become supersaturated with inert gas, and if decompression is too rapid, intravascular bubbles form and tend to lodge in the small veins of the spinal cord (Kamtchum Tatuene et al., 2014) . The result is a venous stasis and infarction: bubbles in the venous plexus obstruct blood outflow, leading to increased pressure, blood-brain barrier disruption, and petechial hemorrhages in the cord. Pathological examinations have indeed found spinal cord lesions consistent with ischemic venous infarcts in severe DCS cases, including perivascular hemorrhages and central cord necrosis (Edmonds et al., 2013). Additionally, direct bubble impingement on nervous tissue and secondary inflammatory injury contribute to the damage. Hallenbeck *et al.* (1975) demonstrated in an animal model that bubble embolization of the spinal cord's venous drainage could reproduce the type of paralysis seen in divers (Saadi et al., 2019). Therefore, the gradual off-gassing from the

spinal cord leads to an ideal environment in which bubbles remain longer, causing extended ischemia relative to other tissues.

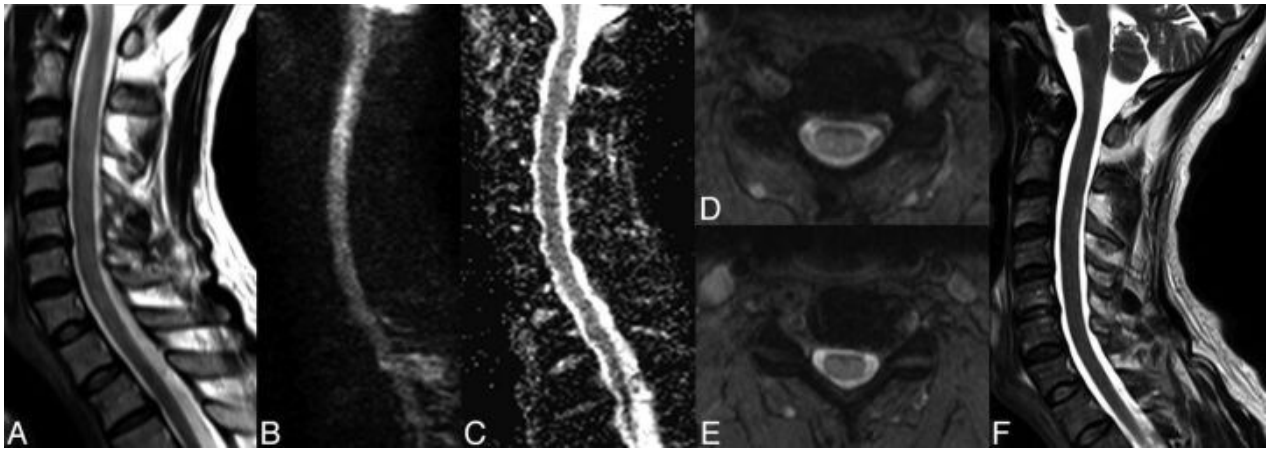

Figure 3. A reversible cervical spinal cord lesion secondary to decompression sickness is depicted. MR imaging reveals an extensive lesion resulting in cervical spinal cord enlargement. The lesion demonstrates hyperintensity on sagittal (A) and axial T2-weighted images (D and E), as well as on diffusion-weighted imaging (B), without a corresponding reduction in signal on the ADC map (C). These imaging findings, along with complete resolution without residual scarring, as confirmed by a follow-up sagittal T2-weighted image (F) taken two weeks later, indicate vasogenic edema, also described as an "ischemic-like" lesion. Picture from Tatuene et al.

Without treatment, spinal DCS can progress rapidly to permanent injury. However, with prompt hyperbaric oxygen therapy (HBOT), a substantial proportion of divers recover fully or partially. Motor function often improves first, followed by sensory; bladder function may take longer. In reported series, many patients show significant improvement after a standard US Navy Treatment recompression and adjunctive therapy, though some require repeated treatments (Naval Sea Systems Command, 2018; Saadi et al., 2019). Unfortunately, a subset of spinal DCS victims are left with residual deficits despite therapy. Chronic paraplegia or paraparesis, if DCS is untreated or treatment is delayed >24 hours, has been documented. Even in those who regain the ability to walk, fine sensorimotor deficits can persist in the long term. Bowel/bladder issues are usually resolved, but in severe cases partial neurogenic bladder may remain. The degree of recovery often correlates with the severity of the initial injury and how quickly recompression was initiated. Fortunately, fatal outcomes from isolated spinal DCS are rare as respiratory centers in the brainstem are not directly affected, but the morbidity can be high. The importance of slow ascents and proper decompression stops to protect the spinal cord cannot be overstated; this is why modern dive tables and computers are calibrated in large part to avoid spinal DCS. (Saadi et al., 2019)

3.3 Inner Ear DCS

Inner ear DCS is a distinct clinical entity within neurological DCI, characterized by predominantly vestibular and cochlear symptoms. It typically occurs after deep, rapid ascents or provocative dive profiles that produce high bubble loads. A classic scenario is a diver who makes a relatively rapid ascent, even from a no-decompression dive, and within minutes to an hour develops violent vertigo and ataxia. Inner ear DCS can be very distressing and dangerous - a sudden loss of balance in the water can lead to drowning if it strikes before the diver is out of the water.

The inner ear's vulnerability is partly due to the supersaturation of the fluids and tissues of the vestibulocochlear apparatus during ascent. The inner ear, particularly the vestibule and cochlea, has a specialized microcirculation and fluid compartments that get rid of the internal gas slowly. It is estimated that inert gas tension in inner ear tissues can remain high for at least 30–40 minutes post-dive, providing a window during which any intravascular bubble can grow or exert damage. Bubbles in the inner ear circulation (e.g. in the internal auditory artery) can either form in situ or arrive via arterial embolism. If a gas bubble enters the inner ear while the tissue is supersaturated, it can rapidly and cause acute dysfunction of the vestibular apparatus (Wilmshurst and Bryson, 2000). In essence, even a small venous embolus that shunts to the arterial side can get stuck the inner ear. The high dissolved nitrogen in the endolymph/perilymph then amplifies the bubble's volume, triggering severe symptoms (Wilmshurst and Bryson, 2000). This explains why inner ear DCS often has a short delay after surfacing – bubbles need a bit of time to transit and then enlarge in the inner ear's supersaturated environment, rather than causing instant symptoms at the surface.

Inner ear DCS usually presents with an acute vestibular syndrome. Within 0.5–2 hours of ascent, the diver experiences rotational vertigo, disequilibrium, and nausea. Nystagmus is observed on examination, and the fast phase of nystagmus often points to the affected ear. Cochlear involvement can lead to tinnitus and sensorineural hearing loss in the affected ear. Some patients describe a feeling of ear fullness or pressure as well. Unlike middle ear barotrauma, inner ear DCS does not typically cause tympanic membrane rupture or middle-ear bleeding, although it may co-occur with middle ear barotrauma if the diver had trouble equalizing during ascent. Because the presentation overlaps with inner ear barotrauma and even labyrinthine artery ischemic stroke, diagnosis relies on the context of decompression stress and, often, the presence of circulating bubbles detected by Doppler or ultrasound or a PFO risk factor (PFO will be discussed in detail in the chapter 4). (Sramek et al., 2022a)

With prompt recompression treatment, inner ear DCS symptoms often improve substantially, especially vertigo. Many divers recover normal balance over days to weeks. However, inner ear DCS carries a risk of lasting vestibulocochlear damage. In some cases, permanent hearing loss (partial) occurs in the affected ear due to hair cell or cochlear nerve damage. Persistent vestibular hypofunction can also happen; the diver may have chronic imbalance or require vestibular rehabilitation exercises. The inner ear is a delicate structure and does not tolerate prolonged ischemia well – if bubbles cause actual hemorrhage in the inner ear (Edmonds et al., 2013) the chances of full recovery diminish. A subset of patients may be left with unilateral vestibular loss, manifesting as continued unsteadiness or need to avoid quick head movements long after the acute DCS is resolved. Fortunately, central compensation often mitigates these deficits over time. The

patent foramen ovale aspect is critical for management: divers who had inner ear DCS are often counseled to get checked for PFO, since closure of a PFO can dramatically reduce the risk of recurrence in those wishing to continue diving. (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024b)

3.4 Peripheral Nervous System

Decompression illness primarily affects the central nervous system, but peripheral nerves can occasionally be involved. Two contexts are relevant: direct bubble impacts on peripheral nerves via the vasa nervorum and secondary peripheral nerve dysfunction due to CNS lesions. True isolated peripheral nerve DCS is rarer than central DCS. When it does occur, it might manifest as a mononeuropathy – for example, an ulnar nerve palsy causing tingling in the ring and little fingers, or a femoral nerve palsy causing weakness in knee extension. Such symptoms could arise if nitrogen bubbles form within or around nerve sheaths, or if decompression-induced intravascular bubbles occlude the tiny nutrient arteries to a nerve trunk. Divers have reported transient limb numbness or weakness that maps to individual peripheral nerves or plexus distributions, which resolved after recompression – suggesting a localized bubble effect on those nerves.
A noteworthy peripheral manifestation is cutaneous decompression sickness, sometimes called *cutaneous nerve syndrome*, where marbling of the skin (cutis marmorata) is accompanied by localized nerve irritation. Cutis marmorata – a mottled skin rash due to venous embolization of skin – is considered a DCS skin manifestation, but it can be associated with burning or tingling in the affected skin area, indicating superficial nerve involvement. This condition has been linked to PFO as well as a harbinger of serious DCS (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024b)

Cranial nerves can also be affected by DCI indirectly. For instance, an infarct in the brainstem due to DCS could cause a cranial nerve palsy such as abducens nerve palsy leading to double vision. There are reports of *trigeminal nerve* numbness after diving, or *optic nerve* involvement leading to visual field defects, but these are usually due to central lesions rather than the peripheral portion of the nerve.(Wilmshurst and Bryson, 2000)

3.5 Outcomes and Recovery

The outcomes of neurological decompression illness are highly variable, ranging from full recovery to permanent neurologic disability. Prognosis depends on factors such as the severity of injury, the specific structures affected, and especially the promptness of treatment. Early recognition and immediate recompression within hours of symptom onset offer the best chance for complete neurologic recovery. In many mild-to-moderate cases of neurological DCS that are treated quickly with hyperbaric oxygen, patients experience dramatic improvement. For example, a diver with spinal DCS who arrives for treatment within a couple of hours may recover the ability to walk within a day or two, with only minor residual numbness. Similarly, inner ear DCS patients often see vertigo resolve during or soon after the first recompression session, though hearing may take longer to improve. (Saadi et al., 2019)

However, in severe or delayed cases, neurological sequelae are common. Spinal cord DCS can leave lasting deficits in a notable subset of patients. Studies have found that despite treatment, a proportion of spinal DCS survivors have persistent motor weakness such as lower extremity paresis or sensory loss months later (Kamtchum Tatuene et al., 2014). One clinical review noted that a normal-appearing spinal cord on initial MRI did *not* guarantee full recovery – about 23% of patients with initially normal scans still went on to have some neurologic sequelae (Kamtchum Tatuene et al., 2014). Conversely, those with obvious cord lesions on MRI often had more severe initial deficits but sometimes showed substantial recovery if treatment was prompt. Importantly, permanent paralysis from diving accidents, while feared, is relatively infrequent in the context of recreational diving thanks to rapid treatment availability. When it does occur, it is often due to either very large bubble loads caused by uncontrolled ascent causing massive AGE plus spinal infarcts or significantly delayed treatment.

Vestibular and cochlear outcomes: Inner ear DCS has a mixed prognosis. Many divers recover balance function entirely, especially with rehabilitation exercises that promote central compensation for any vestibular loss. Nonetheless, some are left with chronic issues such as mild disequilibrium in dark environments or when fatigued. Persistent unilateral vestibular hypofunction can be measured in caloric tests long after an inner ear DCS incident. On the cochlear side, high-frequency hearing loss or tinnitus can be a permanent legacy of inner ear DCS in some cases – likely from hair cell or auditory nerve damage during the insult. In a number of reports, divers with inner ear DCS regained full balance but continued to have a degree of hearing impairment. The extent of recovery seems to depend on whether the insult was primarily ischemic or hemorrhagic: inner ear bubble injury that causes hemorrhage in the cochlea (evidenced by severe hearing loss) often portends incomplete recovery. (Edmonds et al., 2013)

Cognitive and long-term neuropsychological effects: An emerging area of study is the subtle cognitive impact of decompression insults. Even if a diver does not have obvious deficits, there is concern that neurological DCS or repeated subclinical DCS could cause microscopic brain damage that affects cognitive function over time (Jenna Wiley, 2013). Neuropsychological testing of divers with a history of severe DCS has, in some instances, revealed mild impairments in attention, short-term memory, or executive function, although confounding factors must be considered. Moreover, MRI studies of veteran divers with asymptomatic dive histories have shown an increased burden of small white-matter lesions compared to non-divers (Ergen et al., 2017). These lesions are similar to those seen in cerebral small vessel disease and have been correlated with cognitive slowing in other contexts (Filley and Fields, 2016). A 2019 study by Marinella Coco and colleagues used diffusion tensor MRI to examine the brains of 54 professional divers and found subtle white matter changes (decreased fractional anisotropy) predominantly in the frontal lobes, along with slight deficits in attention and memory on cognitive tests (Coco et al., 2019). The cognitive changes were modest but significant, suggesting that repeated exposure to pressure changes, even within safe limits, might cumulatively injure myelinated fibers in the brain (Coco et al., 2019). While this study wasn't specifically about acute DCS, it underlines a concern that neurological DCS could accelerate or compound such effects. In short, divers who have suffered neurological DCS, especially brain involvement, might be at risk for subtle long-term cognitive changes, although many variables such as age, hyperbaric treatment, number of dives play a role and research is ongoing.

Mortality and severe outcomes: Fatalities from neurological DCI are uncommon but can occur, particularly in cases of arterial gas embolism leading to massive stroke or cardiac arrest. An air embolism to the coronary arteries can precipitate an infarction, or to the brainstem can cause respiratory arrest. Dive accident fatality statistics indicate that some fraction of deaths are likely due to arterial gas embolism hitting vital centers (Newton M.D. et al., 2001). Fortunately, most divers survive DCS, and with current treatment protocols, the emphasis is on minimizing morbidity.

3.6 MRI Findings in Decompression Illness

MRI has become a valuable tool for evaluating the neurological impact of DCS, although its sensitivity varies with timing and severity. In the early stages of neurologic DCS, MRI scans are often normal or show only subtle changes, even if the patient is highly symptomatic. Acute gas bubbles themselves are usually too small to be directly visualized on MRI (they may cause artifacts at most), and the initial pathological changes (edema, small infarcts) can be below the resolution of standard imaging or take time to develop. Consequently, a normal MRI shortly after a DCS incident *does not* rule out significant injury. Clinicians have noted cases of definite spinal DCS where the initial MRI showed no abnormalities, yet the patient had objective neurologic deficits. Interestingly, when MRI is normal, the prognosis tends to be better, but as noted, some patients with normal early MRI still develop neurological sequelae later. (Kamtchum Tatuene et al., 2014)

When MRI does reveal DCS-related lesions, the findings can be quite striking. The most typical MRI abnormalities in spinal DCS are T2-weighted hyperintensities in the spinal cord, often affecting the dorsal columns and lateral corticospinal tracts (white matter) and sometimes the gray matter as well (Venkatesh et al., 2013). These lesions reflect edema and ischemia in the regions of bubble-induced injury. In spinal cord DCS, the lesions frequently span multiple vertebral levels and may not conform to a vascular territory in the way a thrombotic stroke would. Instead, one might see patchy, elongated areas of high signal in the thoracic cord. Occasionally, swelling of the spinal cord is present, and gadolinium enhancement can be seen if there is blood-spinal cord barrier disruption. In severe cases, MRI can show extensive cord damage; for example, an MRI might reveal an enlarged, swollen cervical spinal cord with diffuse T2 hyperintensity after an acute DCS hit (Kamtchum Tatuene et al., 2014). Such images correlate with extensive paralysis on exam.

In the brain, MRI findings in DCS can include scattered white matter lesions (hyperintensities on T2/FLAIR) that resemble those seen in chronic small vessel ischemia or demyelination. In acute cerebral arterial gas embolism, diffusion-weighted MRI (DWI) can show acute infarcts – often multiple, small, and disseminated in various arterial territories due to showers of tiny emboli. Some cases of cerebral DCS/AGE have MRI evidence of stroke: for instance, a high signal area in the cortex or deep gray matter on T2 images corresponding to an embolic infarct (Venkatesh et al., 2013). There are also reports of gas appearance on imaging: large gas emboli can sometimes be seen on computed tomography in the brain or even on MRI as void signals in the cerebrospinal fluid spaces, though this is rare and usually in fatal or near-fatal cases (Kamtchum Tatuene et al., 2014). More commonly, any MRI changes in the brain are subtler and may require expert interpretation. In breath-hold divers who suffered neurologic injury (a rare event), MRI has documented ischemic brain lesions as well, underscoring that even in that context MRI can detect DCS-related damage.

3.7 Characteristic findings

When spinal DCS lesions are detected on MRI, they frequently affect the posterolateral regions of the spinal cord, correlating with the high solubility of nitrogen in myelin and the specific venous anatomy of this area. The thoracic spinal cord is particularly often involved.In some cases, imaging aligns with the "venous infarction" concept: MRIs have shown primarily dorsal cord lesions that span multiple levels, which fits with venous drainage patterns rather than a single arterial territory (Kamtchum Tatuene et al., 2014). Brain lesions, if due to PFO-related shower emboli, might show up in watershed areas or scattered in cortex and subcortical white matter.

One interesting MRI finding reported in spinal DCS is reversible spinal cord edema. There are cases where the cord was enlarged with high T2 signal during the acute phase, but follow-up MRI after successful treatment showed resolution of the lesion (Kamtchum Tatuene et al., 2014). This indicates that some DCS lesions represent edema without irreversible necrosis (cytotoxic edema vs. vasogenic), which can completely normalize – correlating with full clinical recovery. On the other hand, lesions that persist on chronic MRI (months later) likely represent permanent tissue injury (gliosis or necrosis). Chronic phase MRI may show residual T2 hyperintensity or atrophy of the spinal cord at the affected levels, corresponding to long-term deficits.

Finally, beyond MRI, other imaging like CT is generally less useful for DCS, except in the immediate setting of AGE where a head CT might rarely show intravascular gas. MRI remains the modality of choice for assessing DCS-related neuroimaging changes. Given the potential for normal early MRIs, the clinical diagnosis of DCS is paramount, and treatment should not be withheld for lack of MRI findings (Kamtchum Tatuene et al., 2014). MRI is best used to document the injury, understand its extent, and possibly to help prognosticate (e.g., multiple spinal lesions might mean a longer recovery). Future research is focusing on standardizing MRI protocols for DCS and improving detection of tiny lesions. Advanced techniques like diffusion tensor imaging and functional MRI may further elucidate the subtler effects of decompression on the brain and spinal cord in the years to come. For now, MRI provides valuable confirmation in many neurological DCS cases and has visually reinforced the long-suspected pathophysiological patterns – for instance, showing those white matter lesions in the spinal cord that mirror the areas of high nitrogen uptake and low perfusion (Kamtchum Tatuene et al., 2014), thus correlating with the biology of decompression illness in the nervous system.

4. Impact of Patent Foramen Ovale (PFO)

One of the most significant individual risk factors for developing serious decompression sickness – especially neurologic DCS and other "unexpected" manifestations – is the presence of a patent foramen ovale (PFO). The foramen ovale is a flap-like opening between the right and left atria of the heart that is normal in fetal circulation but usually seals after birth. In approximately 25% of adults, this closure is incomplete or can reopen under pressure, leaving a potential right-to-left shunt in the heart. Such a shunt means that venous blood and any venous bubbles within it can bypass the pulmonary filter and directly enter the arterial system. This paradoxical embolization is a key mechanism linking PFO to neurological DCS. Arterialized bubbles can lodge in the spinal cord, brain, or inner ear, leading to ischemic damage and neurological symptoms (Cantais et al., 2003a). Neurological DCS manifestations (e.g. limb paralysis, sensory deficits, vestibular disturbances) are thought to arise when gas emboli directly injure central nervous system tissues. In contrast, musculoskeletal DCS (joint pain or dysbaric osteonecrosis) is believed to stem from local bubble formation in tissues and is less dependent on arterial embolization. This explains why a PFO disproportionately increases the risk of serious neurological DCS while having a lesser impact on musculoskeletal DCS. Notably, cutaneous DCS (such as cutis marmorata, a mottled skin rash) is also linked to arterial emboli – studies have shown cutaneous DCS often co-occurs with large PFOs or other shunts. The presence of a PFO can therefore skew the clinical presentation of DCS toward neurological and cutaneous forms by providing a route for venous bubbles to reach sensitive organs like the brain, spinal cord, and skin vasculature.

Beyond PFO, other right-to-left shunts and factors may contribute to bubble arterialization. Intrapulmonary arteriovenous anastomoses can open during exercise or hypoxia, allowing some venous bubbles to pass through the lungs. This mechanism has been proposed as an additional risk factor for DCS even in divers without a PFO. Furthermore, a biophysical model by Arieli and Marmur suggests that bubbles might sometimes form *in situ* within tissues (including the spinal cord) under certain conditions. These alternative pathways notwithstanding, a large PFO remains the most well-documented anatomical shunt associated with neurological DCS. It provides a direct conduit for venous gas emboli that would normally be trapped in the lungs to reach the arterial circulation and vital organs. The result can be catastrophic neurological injury even when dive profiles are relatively benign – so-called "undeserved" DCS hits (Cantais et al., 2003a). In summary, the pathophysiology of PFO-related DCS centers on paradoxical embolization: nitrogen bubbles crossing from venous blood to arterial circulation and causing tissue damage in the central nervous system.

4.1 Epidemiological Link Between PFO and Neurological DCS

Over the past decades, numerous studies have demonstrated a strong epidemiological association between PFO and neurological decompression illness. While a PFO is common in the general population (~1 in 4 people), it is disproportionately prevalent among divers who suffer neurological DCS (Peppas et al., 2023). A recent meta-analysis encompassing 9 studies (1830 divers) found that 62.6% of divers with neurological DCS had a right-to-left shunt, compared to only 27.3% of divers without DCS. This translates to roughly four-fold

increased odds of neurological DCS in the presence of an RLS (odds ratio ~3.8, 95% confidence interval 2.8–5.3). Moreover, the risk appears to escalate with larger shunts: high-grade shunts were about five times more common in the DCS group than in controls (57.8% vs 18.4%, OR ~4.98). Notably, divers with inner-ear (cochleovestibular) DCS – a particularly severe neurological manifestation – show an even stronger association with PFO, with reported odds ratios exceeding 10 for PFO presence (Peppas et al., 2023). These data underscore that divers who experience neurological DCS are far more likely to have a PFO than those who dive without incident.

Earlier case-control and cohort studies yielded similar findings. For instance, Cantais et al. (2003) observed that divers who suffered cerebral or inner-ear DCS had a significantly higher incidence of large shunts, concluding that a major right-to-left shunt was associated with increased risk of these neurological DCS forms (Cantais et al., 2003b). In a cohort of 230 divers studied by Torti et al. (2004), 27% were found to have a PFO; those with PFO had a markedly higher history of DCS events (29% of PFO-positive divers vs 6% of PFO-negative divers had experienced a serious DCS) (Torti, 2004). The incidence of major DCS per dive was 4.8–12.9 times higher in divers with PFO than in those without. Importantly, Torti's study also demonstrated a dose-response effect: the risk of severe DCS increased with larger PFO size, implicating bigger shunts in more frequent or more severe hits. These findings were among the first to directly quantify the risk: the odds of a major DCS were roughly five times greater in divers with a PFO, despite an overall low absolute risk per dive (Torti, 2004). Consistent results have been reported by Wilmshurst and colleagues, who linked unexplained cutaneous DCS to RLS (often PFO), and by other investigators who found PFO present in a majority of unexplained neurological DCS cases (Peppas et al., 2023). Collectively, the epidemiological evidence firmly supports PFO as a significant risk factor for neurological decompression illness. While factors such as dive depth, rapid ascents, age, sex, and body mass may also influence DCS risk, the presence of a PFO appears to be one of the most critical determinants of whether a given dive leads to neurological injury (Honěk et al., 2019; Sramek et al., 2022b).

4.2 RLS Grade and Neurological DCS Risk Stratification

The magnitude of right-to-left shunting through a PFO (often graded by contrast echocardiography or transcranial Doppler) has a profound impact on DCS risk. High-grade shunts, which allow a large volume of bubbles to transit, confer the greatest danger. In the study by Šrámek et al. (2022) – a comprehensive risk stratification of neurological DCS in divers – this relationship was quantified in detail. Among 640 divers screened with transcranial Doppler, 258 (40.3%) had evidence of an RLS (any grade). Neurological DCS was reported in 17.1% of divers with an RLS, compared to only 1.3% of those without any shunt (a highly significant difference, $p<0.001$) (Sramek et al., 2022b). Put another way, divers with a PFO were over ten times more likely to suffer neurological DCS than those with no shunt. This aligns with the adjusted hazard ratio of approximately 12 found in Šrámek et al.'s survival analysis for the effect of RLS presence on time to DCS onset. The incidence of neurological DCS per dive was likewise dramatically higher in the RLS-positive group (on the order of 7 cases per 10,000 dives) compared to the RLS-negative group (~0.6 per 10,000 dives)

– an order of magnitude difference reflecting the same hazard ratio (Sramek et al., 2022b). These findings provide robust statistical evidence that a PFO greatly increases the risk of an acute neurological DCS event in divers, even when controlling for other factors.

Crucially, Šrámek et al. (2022) demonstrated a clear risk stratification according to shunt size (grade). Divers were categorized by RLS grade as low, medium, or high, with high-grade shunts further subdivided into those occurring only with a Valsalva maneuver versus those present at rest. The proportion of divers experiencing neurological DCS rose sharply with increasing shunt grade. In fact, only about 4–5% of divers with a *low-grade* RLS had any history of neurological DCS, whereas over 57% of divers with a high-grade RLS visible at rest had suffered at least one neurological DCS episode. High-grade shunts detectable at rest represent the most severe end of the spectrum – effectively an open conduit allowing massive bubble transit without provocation. Even high-grade shunts that only manifested during straining (Valsalva) carried substantial risk, though intermediate between the low and spontaneously large shunts (exact percentages for medium and high-with-Valsalva were reported to be between those extremes). The gradation is intuitive: larger shunts permit more bubbles to reach arterial circulation, increasing the likelihood of CNS embolization. Šrámek et al. quantified this with a hazard function analysis, confirming that higher RLS grades correlate with progressively shorter latency to DCS and greater cumulative incidence. Their data solidify the concept of risk stratification by PFO size – a diver with a small, occasional shunt has relatively low risk, while a diver with a large persistent shunt faces a dramatically elevated probability of neurological DCS. These results have led the authors to advocate for routine TCD screening to identify high-risk divers (those with large shunts). Although such screening and subsequent interventions are debated, the evidence suggests that knowing a diver's shunt grade can inform the understanding of their susceptibility to neurological injury (Sramek et al., 2022b).

Interestingly, the Šrámek et al. study also shed light on which types of DCS incidents are predictive of an underlying PFO. In their analysis of various DCS manifestations, only cutaneous DCS (skin marbling or rash) was significantly associated with later neurological DCS, with an adjusted hazard ratio of ~2.8. Of 84 divers in their cohort who had experienced cutaneous DCS, 20 (24%) later suffered neurological DCS. This finding reinforces prior hypotheses that cutis marmorata in divers often results from venous bubbles passing through a PFO into the arterial circulation (effectively a mild cerebral embolization) (Cantais et al., 2003a). Skin DCS can thus be a harbinger of a significant shunt and future neurological hits. In contrast, musculoskeletal DCS (joint pain) did not show a significant association with subsequent neurological DCS in their data, which is consistent with musculoskeletal symptoms often arising from local tissue bubbles rather than arterial emboli. Taken together, these nuances underscore the central role of PFO-mediated embolization in the pathogenesis of neurological DCS: the larger the shunt, the higher the risk, and even seemingly benign DCS symptoms like a skin rash may indicate the presence of a dangerous shunt.

4.3 Recurrent Neurological DCS in the Presence of PFO

An important clinical implication of the PFO–DCS link is the risk of recurrent incidents. Divers with a PFO who continue to dive after an initial DCS are at a heightened risk of suffering repeat neurological DCS events. Gempp et al. (2012) conducted a case-control study specifically examining risk factors for recurrent neurological DCS in experienced divers. They found that the presence of a large RLS was a strong independent

predictor of recurrence: divers with a large PFO had an odds ratio of about 5.4 for a repeat neurological DCS compared to those without a shunt (95% CI 1.5–19.7, *p*=0.006). In fact, PFO was one of the top risk factors identified, alongside lack of changes in diving practice after the first event (E. Gempp et al., 2012). This suggests that if a PFO remains open and the diver's behavior is unmodified, the likelihood of another hit is considerably elevated. Šrámek et al. (2022) similarly noted that many of their RLS-positive divers had multiple DCS episodes. Although their 2022 study focused on first-event risk via survival analysis, the high proportion of neurological DCS cases in the high-grade shunt group implies a tendency toward recurrent problems if the shunt is not addressed (Sramek et al., 2022b). Indeed, historical series have reported that a majority of divers who suffered unexplained (unprovoked) DCS and kept diving went on to have additional DCS events, unless mitigating actions (like PFO closure or more conservative dive profiles) were taken (E. Gempp et al., 2012).

Conversely, evidence from intervention reinforces the causal link between PFO and recurrence. In a recent longitudinal study, divers with high-grade PFOs underwent PFO closure and were followed over a mean of 6.5 years; notably, none of the divers who had their PFO closed experienced DCS during follow-up. By comparison, those who kept diving with a PFO (but perhaps with more caution) had a reduction in DCS incidence but not elimination of risk (Honěk et al., 2022). While this was not a randomized trial, the stark absence of DCS after closure provides compelling support that the PFO was the principal driver of those divers' prior neurological events. It mirrors earlier observations by Billinger et al. (2011), who reported fewer brain lesions on MRI and no further neurologic DCS in divers after PFO closure, versus continued incidents in those who did not close the shunt (Torti, 2004). In summary, PFO not only predisposes divers to an initial neurological DCS, but if left uncorrected, it significantly elevates the risk of recurrence with subsequent dives. This epidemiological and clinical evidence solidifies the pathophysiological link: the presence of a PFO creates a persistent vulnerability in divers, whereby each dive carries an outsized risk of CNS embolization and injury. Avoiding recurrent neurological injury in such cases fundamentally requires addressing the shunt or altering dive behavior – further underscoring how central the PFO is to the pathogenesis of neurological decompression illness.

The convergence of pathophysiological understanding, clinical observation, and epidemiological data makes it clear that a patent foramen ovale can dramatically increase the risk of neurological decompression sickness. Large right-to-left shunts facilitate the arterialization of venous gas bubbles, leading to brain and spinal cord insults that manifest as serious DCS symptoms. Divers with significant shunts experience neurological DCS at rates far exceeding their peers, and this risk climbs with larger shunt size. They are also more prone to repeated hits over time. These findings, grounded in studies like Šrámek et al. (2022) and supported by a host of other investigations, illuminate the pathophysiological and epidemiological link between PFO and neurological DCS. In the context of decompression illness, a PFO serves as a direct pathway for injury, explaining why harmless venous bubbles would otherwise become neurologically deleterious in a subset of divers. This knowledge has informed risk stratification efforts and provides a biological rationale for considering PFO status in the evaluation of divers with neurological DCS, all while stopping short of clinical management recommendations in this discussion. The presence of a PFO transforms the risk landscape of diving by introducing a latent hazard for the most severe forms of DCS, thereby playing a pivotal role in the pathophysiology of decompression illness in the nervous system.

5. Molecular and Pathophysiological Mechanisms

Transcriptomic and molecular studies in DCS reveal a robust activation of immune, inflammatory, and coagulation pathways at the genetic level (Madden et al., 2023; Magri et al., 2021b). Key features include neutrophil and monocyte activation, upregulation of cell adhesion molecules facilitating leukocyte-endothelial interactions, complement and cytokine release, and evidence of oxidative stress handling. These findings are congruent with what physiological and histological studies have shown, bringing a cohesive picture from the molecular scale to the whole-organism scale. They open the door to new diagnostic tools and therapies – for example, perhaps a drug that can suppress neutrophil degranulation or adhesion could ameliorate DCS injury (some have considered statins or NSAIDs for such purposes). While diving medicine has traditionally focused on tables and oxygen, the future may integrate molecular diagnostics to personalize DCS risk management.

5.5 Peripheral Blood Transcriptome and Molecular Mechanisms

In recent years, scientists have turned to genomic and molecular tools to better characterize the body's response to decompression stress. One such approach is examining the peripheral blood transcriptome – the complete set of RNA transcripts (gene readouts) in blood cells – to see how gene expression changes after diving and in DCS. This line of research aims to identify which biological pathways are activated or suppressed by decompression, providing insight into molecular mechanisms and potential biomarkers.

A 2021 study by Magri et al. (Pace *et al.*) looked at the gene expression profiles of white blood cells in divers who suffered DCS compared to those who had uneventful dives (Magri et al., 2021b). Blood samples were taken within 8 hours after the dive (when DCS symptoms were present in the affected divers) and again about 40–44 hours later, after treatment with hyperbaric oxygen. The transcriptome analysis revealed that divers with DCS had a distinct pattern of gene expression acutely: there was an enrichment of transcripts related to acute inflammation and innate immune activation, with significant upregulation of genes involved in neutrophil activation, degranulation, and pro-inflammatory signalling (Magri et al., 2021b). In particular, pathways such as those regulated by NF-κB and cytokines were highlighted, and many of the top differentially expressed genes were neutrophil-associated. This aligns well with the physiological understanding that DCS provokes inflammation and that neutrophils play a key role in bubble-induced injury (Madden et al., 2023). By the second time point (~40 hours and post-treatment), the gene expression differences largely subsided – the DCS patients' gene profiles had shifted closer to those of the control divers. This suggests that the hyperbaric oxygen therapy (and time) helped normalize the immune activation. Interestingly, even the divers who had uneventful dives (no DCS) showed some gene expression changes after diving, but these were much milder; thus, there is a continuum of physiological stress from normal dive to DCS, rather than an all-or-none response (Magri et al., 2021b).

Further analysis in that study indicated that certain clusters of co-expressed genes were specifically tied to myeloid cells (neutrophils, monocytes). At the onset of DCS, gene clusters related to neutrophil activation were strongly upregulated. These included genes for components of neutrophil granules (enzymes like proteases, components of the oxidative burst, etc.) and cell surface markers indicating activation. One

identified cluster was enriched in transcripts characteristic of CD11b+ neutrophils and inflammatory monocytes (Magri et al., 2021b). Essentially, the data paints a picture of DCS causing a surge in innate immune activation – the body essentially thinks it's dealing with a major injury or infection and turns on the genes accordingly. Notably, many of these inflammatory pathways overlap with those seen in conditions like sepsis or trauma, although in DCS the trigger is bubbles.

Parallel to gene expression, researchers have also examined changes in protein expression and molecular markers in blood post-dive. It was already mentioned that cytokines such as IL-6 being elevated after decompression even without DCS. Inflammatory cytokines (IL-1β, TNFα, IL-8, etc.) have been measured in animal models: for example, a rat model study by Bigley et al. (2008) showed increases in IL-1β and IL-6, as well as cell adhesion molecules like ICAM-1 (intercellular adhesion molecule-1) and P-selectin in decompressed rats (Magri et al., 2021b). These adhesion molecules, expressed on endothelial cells and leukocytes, facilitate the recruitment of neutrophils and platelets to sites of injury – their upregulation in DCS models indicates the body is signalling immune cells to attach to blood vessel walls and perhaps migrate into tissues, contributing to inflammation. Elevated ICAM-1 can make the endothelium "stickier," promoting the formation of neutrophil aggregates on bubble surfaces or damaged endothelium, as was observed in experiments (Department of Anaesthesiology, School of Medicine, University of Auckland, Auckland, New Zealand et al., 2024a).

Another interesting molecular player is the complement system. Decompression has been shown to activate complement; divers after a dive have demonstrated increased levels of complement activation products like C5a (Madden et al., 2023). C5a is a potent attractant and activator of neutrophils, which ties back into the gene findings of neutrophil activation.

The coagulation and fibrinolysis genes have also been examined. Some studies have looked at mRNA levels for coagulation factors or anticoagulant proteins after diving. One finding (Rocco et al. 2018) was that decompression can affect the expression of genes related to hypoxia and coagulation in circulating cells. In addition, the discovery of bubble-induced tissue factor release suggests that monocytes might be expressing more tissue factor post-dive, again promoting coagulation (Madden et al., 2023).

A concept related to transcriptomics is identifying a "gene signature" that could serve as a biomarker. If, say, a set of 10 genes is reliably up or downregulated in DCS cases but not in clean dives, that could form the basis of a gene expression panel to diagnose DCS or gauge its severity. The DAN article on DCS biomarkers alludes to using gene expression profiling (microarrays) to find such signatures (Dawn Kernagis, et al., 2015). The challenge is that diving itself causes changes, so one must distinguish normal dive response from pathological DCS response(Magri et al., 2021b). The Pace et al. study addressed that by comparing DCS vs matched controls and found clear differences, giving hope that transcriptomic biomarkers could be developed.

Cell adhesion molecules (CAMs) and endothelium: The mention of cell adhesion molecules in the question likely refers to the crucial role of the vascular endothelium in DCS. The endothelium responds to bubbles by upregulating adhesion molecules like ICAM-1, VCAM-1, and E-selectin, which cause leukocytes to stick to the vessel wall (Magri et al., 2021b). This can lead to leukocyte sequestration and plugging in capillaries,

compounding ischemia. It can also initiate an inflammatory cycle where the stuck white cells release enzymes and free radicals that injure the endothelium further. One study (Henderson et al. 2008, as referenced by Bigley) specifically demonstrated increased levels of circulating soluble ICAM-1 and elevated expression of E-selectin in a rat model of DCS, indicating endothelial activation. So at a molecular level, part of DCS pathophysiology is analogous to vascular injury or vasculitis, with bubbles serving as the insult that turns on the adhesion cascade.

Microparticles and extracellular vesicles: microparticles were discussed earlier in pathophysiology, but from a molecular standpoint, these vesicles often carry specific surface markers. For example, endothelial microparticles (EMPs) might carry ICAM-1 or VE-cadherin fragments; platelet microparticles carry P-selectin or GPIIbIIIa fragments. After diving, the pattern of microparticles can be profiled – e.g., studies have shown increases in endothelial-derived microparticles after decompression, suggesting endothelial cells are getting activated or damaged and shedding vesicles (Madden et al., 2023). These microparticles in turn can be measured and even have genetic material inside them (like microRNAs) that might reflect what processes are happening in the parent cells.

Oxidative Stress Pathways: Another molecular aspect is oxidative stress. Bubbles can lead to reperfusion-like injury, so genes like heme oxygenase-1 (HO-1) or superoxide dismutase (SOD) might be upregulated as part of a defensive response. The transcriptome study noted enrichment of “free radical scavenging” pathways in the DCS group (Magri et al., 2021b), which implies that antioxidant responses were activated. This is possibly an adaptive attempt to counteract reactive oxygen species generated by neutrophils and ischemia. This ties into findings from other decompression experiments where markers of oxidative stress, like malondialdehyde or oxidized glutathione, were elevated.

Implications of Molecular Research: Understanding these molecular changes helps in a few ways. First, it reinforces and refines our understanding of DCS pathophysiology – for instance, seeing a neutrophil gene signature confirms that neutrophils are key players. Second, it identifies potential targets for intervention: the knowledge that certain inflammatory pathways are critical and can lead to tests using drugs that modulate those IL-1 blockers or complement inhibitors to reduce DCS injury. Third, it provides potential biomarkers: for example, a combination of certain cytokine levels or specific microparticle counts might predict which divers are at risk of DCS or have incurred significant decompression stress.

5.2 Role of D-Dimers as Biomarkers

In the search for objective measures to assess decompression stress and DCS severity, D-dimer has emerged as a promising biomarker related to the coagulation changes in DCS. D-dimer is a fibrin degradation product – essentially a small protein fragment present in the blood when fibrin blood clots are formed and subsequently broken down. Clinically, D-dimer is commonly used to aid in diagnosing thrombotic events, such as deep vein thrombosis or pulmonary embolism, because elevated D-dimer indicates recent or ongoing clot formation and lysis.

The rationale for using D-dimer in DCS comes from the recognition that bubbles can activate the coagulation system, leading to microthrombi and clot formation in severe cases of DCS. If clotting is triggered, the fibrinolytic system will begin to break down clots and release D-dimers into the circulation. Indeed, coagulation activation has been noted in many cases of decompression illness – sometimes mild and localized, other times more disseminated in severe DCS. In extreme cases of neurological DCS, clinicians have observed laboratory signs consistent with a low-grade disseminated intravascular coagulation, such as thrombocytopenia and elevated clotting markers, suggesting that intravascular clotting is part of the pathology. This provided a clue that measuring byproducts of clotting like D-dimer might reflect the severity of DCS. (Emmanuel Gempp et al., 2012)

A key study by Gempp et al. (2012) investigated the value of plasma D-dimer levels in predicting the severity of neurological DCS in divers. In this study of 84 divers treated for neurological DCS, blood samples were taken within 8 hours of symptom onset and analyzed for D-dimer, fibrinogen, and platelet count. The neurological DCS cases were scored for initial severity using a standardized clinical scoring system, and outcomes were assessed at 3 months (whether the diver had complete recovery or persistent neurological sequelae). The results are showing that about 26% of these cases had incomplete recovery (i.e. lasting deficits), and those divers had significantly higher D-dimer levels on presentation than those who fully recovered. In multivariate analysis, an elevated D-dimer was independently associated with a greater risk of neurologic sequelae. Other coagulation variables as fibrinogen levels and platelet counts, did not show a significant difference between those with good vs. poor outcomes. Importantly, the study found that combining the information from the initial clinical severity score with the D-dimer test result provided a better prognostic accuracy than either alone. Specifically, using a cutoff D-dimer value of 0.40 mg/mL, if a patient had a severe clinical presentation *and* a positive D-dimer, the post-test probability of that patient having a poor outcome was very high. In practical terms, a diver with a neurologic DCS event who shows a high D-dimer level is more likely to suffer long-term impairment, signalling the need for perhaps more aggressive or adjunctive treatment and closer follow-up.(Emmanuel Gempp et al., 2012)

This finding aligns with the concept that DCS-related coagulopathy contributes to tissue injury. D-dimer here is acting as a marker of the body's attempt to dissolve intravascular fibrin clots that presumably formed due to bubble-induced endothelial damage and clotting activation. A higher D-dimer suggests more clot formation was taking place, which likely corresponds to more severe intravascular trauma by bubbles. The link between elevated D-dimers and neurological DCS has been corroborated by other observations as well. For example, an anecdotal report noted divers with very severe DCS showed signs of a low-grade DIC, of which D-dimer is a hallmark. (Emmanuel Gempp et al., 2012).

Beyond prognostication, could D-dimer be used for diagnosis or early detection of DCS? In theory, a blood test that becomes positive early in DCS could supplement clinical judgment. However, DCS is a clinical diagnosis and typically requires prompt treatment without waiting for lab results. D-dimer testing could be useful in a hospital setting when evaluating a patient post-dive, particularly if the diagnosis is in doubt or if one wants to gauge severity. In most dive accidents, though, treatment would not be withheld for a biomarker result. One scenario where D-dimer might play a role is in triaging patients in remote or mass casualty situations – for instance, if multiple divers were bent and resources are limited, those with high D-

dimer might be prioritized for treatment as they likely have more severe DCS.

It's also important to recognize the limitations of D-dimer. D-dimer is not specific to DCS; many conditions like recent surgery, trauma, bleeding, even normal exercise to some extent) can raise D-dimer levels. In the diving context, a diver who had an injury or a medical condition could have an elevated D-dimer unrelated to DCS. Moreover, the timing of the test in relation to the DCS event matters – if done too early, the clot breakdown might not have generated much D-dimer yet; too late, and treatment or natural resolution might have normalized levels. In the study by Gempp et al., samples were taken within 8 hours of surfacing, which appears to be a good window to capture the peak D-dimer.

Other biomarkers of neurological injury have been explored alongside D-dimer. For example, the protein S100β (a marker of CNS injury) has been shown to rise in some animal models after rapid decompression. Neuron-specific enolase (NSE) and other brain injury markers have also been considered. Creatine phosphokinase (CPK), a general tissue damage enzyme, was noted to elevate in some DCS subjects, especially those with arterial bubbles. Brain natriuretic peptide (BNP) was found to increase in divers after long dives, possibly related to cardiovascular strain. However, none of these have been as directly tied to outcomes as D-dimer has in the case of neurological DCS. So far, no single biomarker has gained universal acceptance for DCS diagnosis or prognosis, but D-dimer stands out as one of the more promising candidates for reflecting the pathophysiological severity of an episode (Dawn Kernagis, et al., 2015).

6. Discussion

This study offers a comprehensive overview of decompression illness (DCI), elucidating both its mechanical foundations and its complex pathophysiological impacts on the nervous system. It integrates foundational gas laws with clinical, molecular, and epidemiological evidence to contextualize decompression sickness (DCS) and arterial gas embolism (AGE) within a modern biomedical framework. Of particular emphasis is the central nervous system, which remains disproportionately vulnerable to decompression-related injuries due to its unique vascular and metabolic characteristics.

Mechanistically, the research confirms that DCI is initiated by supersaturation of inert gases during rapid decompression, leading to bubble formation within tissues and vasculature. These bubbles not only disrupt local blood flow but also elicit endothelial damage, coagulation, and immune activation. This aligns with previous experimental and clinical literature suggesting that DCI is not solely a physical phenomenon but a biologically active process involving inflammation, oxidative stress, and molecular signalling cascades.

The findings presented in Chapter 5 advance the understanding of DCI through molecular insights, particularly regarding peripheral blood transcriptomics and biomarkers such as D-dimers. Elevated D-dimer levels observed in affected individuals suggest systemic endothelial activation and thrombotic risk, corroborating their utility as prognostic indicators (Gempp et al., 2012). Furthermore, upregulation of genes associated with neutrophil activation and adhesion molecules supports the view that DCI pathogenesis includes immune-mediated endothelial injury (Magri et al., 2021a).

Another debated topic is the clinical significance of subclinical white matter hyperintensities in divers without symptomatic DCS. While some MRI studies (Coco et al., 2019) suggest cumulative injury even in “safe” divers, others argue these findings overlap with age-related small vessel disease and need longitudinal validation. This highlights the complexity of diagnosing DCS-related brain injury in asymptomatic individuals and reinforces the need for long-term cognitive and imaging follow-up.

Crucially, the thesis emphasizes the role of anatomical anomalies—specifically, a patent foramen ovale (PFO)—as critical risk factors for severe, especially neurological, DCI. Chapter 4, grounded primarily in the 2022 study by Šrámek et al., illustrates the strong epidemiological correlation between right-to-left cardiac shunts and central nervous system manifestations of DCS. The Šrámek cohort (n = 640) revealed a tenfold increase in neurological DCS among individuals with PFOs compared to those without shunts. Additionally, the risk of DCS was stratified by shunt size, with large spontaneous shunts associated with a >50% incidence of neurological symptoms. The discussion also incorporates the concept of clinical phenotypes of DCS, noting that skin manifestations such as cutis marmorata may serve as early indicators of underlying PFO. This reinforces the need to reevaluate seemingly benign presentations, particularly in individuals who exhibit multiple or recurrent DCS episodes. Furthermore, the cumulative risk for divers with untreated PFOs supports the hypothesis that anatomical defects constitute a persistent predisposition for embolic injury, especially when coupled with provocative dive profiles.

There is broad agreement on the need for early treatment, with hyperbaric oxygen therapy demonstrating strong efficacy, especially within 6 hours of symptom onset. However, research gaps persist regarding

optimal recompression protocols, adjunctive therapies (e.g., steroids, neuroprotectants), and long-term cognitive outcomes. Questions also remain about individual susceptibility: why do some divers with similar exposures develop DCS while others remain unaffected? Genetic studies and inflammatory biomarker profiling may help unravel this variability.

This work expands the classical understanding of DCI by integrating molecular markers and anatomical predispositions into the broader clinical narrative. It supports a shift toward risk stratification and personalized assessment, recognizing that decompression injury arises not only from external environmental factors but also from internal physiological and genetic susceptibilities.

Finally, the thesis highlights the necessity of multidisciplinary research—combining diving physiology, neuroimaging, molecular biology, and clinical follow-up—to build a predictive model of DCS risk and improve post-dive screening. Preventive strategies, including PFO closure and dive behavior modification, show promise but require individualized application based on diver history and risk tolerance.

7. Conclusion

This thesis consolidates current knowledge on decompression illness, bridging classical physical gas law theory with contemporary insights from vascular biology, molecular medicine, and neuroepidemiology. Decompression sickness, traditionally regarded as a disorder of gas bubble dynamics, is increasingly understood as a multifaceted syndrome involving mechanical, thrombotic, immunologic, and neurological elements.

Key conclusions include:

1. Multifactorial Pathogenesis: DCI arises from a combination of physical bubble formation and biological response. Intravascular bubbles induce endothelial damage, activate inflammatory pathways, and contribute to tissue hypoxia, especially in the brain and spinal cord.

2. Neurological Susceptibility: The central nervous system is disproportionately affected by decompression insults, with neurological DCS manifesting as cerebral ischemia, spinal cord injury, or vestibular dysfunction. The severity and prognosis of these manifestations depend on both bubble burden and individual susceptibility.

3. Role of Patent Foramen Ovale: A PFO constitutes a major risk factor for neurological DCS. Evidence from Šrámek et al. demonstrates a dose-response relationship between shunt size and DCS risk, particularly for high-grade RLS. These findings underscore the importance of anatomical screening in divers with unexplained or recurrent DCS.

4. Molecular and Biomarker Correlates: The detection of D-dimers and transcriptomic shifts offers promising avenues for non-invasive evaluation of decompression stress. These biomarkers can potentially enhance diagnostic accuracy and guide management decisions in clinical settings.

Neurological decompression sickness constitutes a critical subset of dive-related injuries with potentially irreversible outcomes. While recompression therapy can often reverse early deficits, the severity and duration of symptoms, particularly in spinal and cerebral DCS, may lead to long-term disability. Inner ear and peripheral nervous system involvement, although rarer, further complicate diagnosis and management. Advances in molecular diagnostics and imaging have improved our understanding, but clinical decision-making still relies heavily on symptomatology and risk factor identification.

This thesis underscores the need for heightened awareness among clinicians and divers about individual predispositions such as PFO and emerging biomarkers. Existing literature reveals both areas of consensus and significant variability, particularly in diagnostic imaging and recurrence prediction. Future studies must address these inconsistencies, ideally through prospective trials incorporating imaging, neurocognitive testing, and molecular assays.

In conclusion, understanding the multifaceted pathophysiology of neurological DCS is essential for optimizing prevention, early diagnosis, and targeted therapy. As research progresses, integrating clinical, anatomical, and molecular data will be pivotal in shaping personalized diving medicine strategies and improving outcomes in this complex disorder. The findings of this work contribute to the evolving understanding of decompression illness and offer a foundation for future research into personalized diving medicine, risk prediction models, and targeted interventions for high-risk populations.

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