Research Article

The Gradient Perfusion Model Part 1: Why and at what sites decompression sickness can occur

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ABSTRACT

Introduction: Decompression sickness (DCS) is manifested by the quantity and location of bubbles in body tissues after reduction in ambient pressures. Models have been formulated to explain why bubbles form, but none provide satisfactory explanations as to why the findings of DCS occur as they do. This first of a three-part series explains why and at what sites DCS occurs.

Materials and Methods: Over a 50-year span and 500 cases of DCS we have managed, it has become apparent that almost all "unexplained DCS" (i.e., cases with no obvious explanation as to how/why they occurred) have physiological explanations. The vagaries of the physiology of tissue perfusion and the physics of gradients as a cause of autochthonous bubble formation were analyzed.

Findings: Perfusion is highly variable, with so-called "fast" tissues (i.e., tissues with a rapid rate of saturation) requiring a constant blood supply, "intermediate" tissues requiring a blood supply proportional to needs, and "slow" tissues having minimal perfusion requirements. The 5-liter blood volume in a vascular system with greater than a 20-liter capacity requires careful regulation. Disruptions in the regulation and/or overwhelming gradients explain why DCS occurs.

Conclusions: Our Gradient-Perfusion Model provides an explanation as to why disordering events account for almost all cases of unexplained DCS. We propose that this latter term be discarded and "disordering events" be used for DCS cases that have no obvious explanations.

KEYWORDS: Gradient-Perfusion Model; decompression sickness; unexplained DCS; fast tissues; disordered decompression; fast, intermediate and slow tissues

INTRODUCTION

Decompression sickness (DCS) deserves to be considered a syndrome because of its collection of symptoms and diverse presentations. Many hypotheses attempt to explain their underlying causes (Table 1) [1-22]. However, no model uniformly accounts for all the causes or the clinical presentations of DCS, but bubbles are always an integral part of the pathophysiology. Once bubbles become present in tissues, pathophysiological mechanisms include platelet deposition with activation of the coagulation mechanism, endothelial dysfunction, capillary leakage, complement inflammation, leukocyte-endothelial interactions and, possibly, microparticles. These processes provide explanations for the manifestations of DCS when the bubbles occur in the blood vessels. Our organelle (Ruffini Type-2 corpuscle) and adventitial microscopic bubbles hypothesis provides an explanation for juxta-articular and non-anatomical neurological pain presentation. Nonetheless, predictable clinical findings typically occur under identifiable circumstances. The common denominator for all the manifestations is inert gas bubble formation in tissues [23].

In 1989 Wienke described his Reduced Gradient Bubble Model (RGBM), which rapidly gained acceptance and became the basis for the algorithms used in the majority of the modern scuba diving computers [13]. Wienke recognized that a "free gas phase" tissue compartment needed to be considered with inert gas exchange. In this tissue compartment inert ongassing and offgassing is far faster than the previously accepted five-minute tissue half-time that was used to compute decompression tables.

TABLE 1. SUMMARY OF DECOMPRESSION MODELS

Model	Year	Concept	Details
Neo-Haldanian Models			
Workman[1]	1957	M-value	9 hypothetical compartments with half-times between 5 and 240 minutes. Maximum tissue tensions varied linearly with depth; the critical supersaturation ratios were a function of the ambient pressure. 27 parameters for air tables and 27 for heliox tables.
Bühlmann[2]	1965	Gas sequencing	Half-times for nitrogen/helium following a 2.6:1 supersaturation ratio. Several test series carried out in hyperbaric chambers. A decompression model widely applied in recreational diving.
French Navy[3]	1977	Oversaturation ratios for each tissue constant with pressure	Quantified the maximum allowable supersaturation states of five hypothetical tissues.
COMEX[4]	1992	M-value with infinite number of theoretical compartments	MT92 tables and procedures, including heliox saturation, were built for air, air + oxygen and heliox + oxygen decompressions.
Diffusion-Limited Tissue Models			
Hempleman[5]	1952	Joints as target tissues	Joint pain decompression sickness precedes neurological symptoms. Simplified model being a semi-infinite cartilage slab with a one-dimensional diffusion process. Limited to moderate- to short-duration exposures.
Hill[6]	1966	Deep stops. Zero supersaturation	The rate of the first part of decompression had to be reduced with a deep first stop to slow down the tissue-to-blood gas exchanges.
DCIEM[7,8] **(Kidd-Stubbs)**	1993	4 slabs of tissue connected in series	A more complex mathematical formulation of gas exchanges by both perfusion and diffusion than a simple perfusion approach considering only independent compartments.

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The free gas phase occurs in ultra-fast tissues, where ongassing and offgassing occur almost instantaneously with changes in ambient pressure in tissues such as the bloodstream and the lungs.

Even though its predominant application is in the prevention of DCS, it provided an explanation for the cause of bubble formation and contributed to the dictums to reduce ascent rates to 1 foot every two seconds (versus the U.S. Navy rule of 1 foot every second) and the execution of a three-minute "safety stop" at the 15-foot level for each scuba dive ascent. As well accepted as the Wienke RGBM is, it does not fully explain why bubbles form in the locations they do, nor provide guidance for management of DCS.

Regardless, several deductions can be made from the hypotheses as to why bubbles form. *First*, bubble formation is fundamental to the definition of decompression sickness. *Second*, the amount of ongassing into tissues is a function of their perfusion coupled with the partial pressure of the inert gas breathed and the duration of exposure. *Third*, the gradients for bubbles to nucleate and the adequacy of perfusion to offgas body tissues supersaturated with inert gas determine whether DCS occurs – i.e., the Strauss Gradient-Perfusion Model.

The carbonated soda bottle analogy explains many decompression science observations. Body tissues, like the undisturbed carbonated soda bottle, can tolerate supersaturation of the dissolved inner gases without forming bubbles. When perturbed (i.e., disturbance of motion, course, arrangement or state of equilibrium), bubbles form, as in shaking the soda bottle. Perturbing events can include:

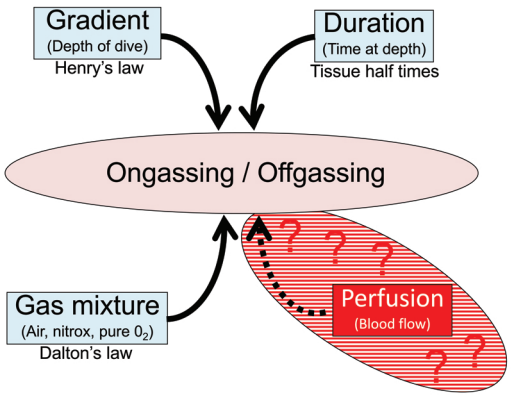
1) Overwhelming gradients (e.g., with reductions in ambient pressure);
2) Physical stresses (such as shaking/vibrating the soda);
3) Elevated temperatures (i.e., bubble enlargement à la Charles's law; and
4) Chemical/physical chemical causes which may act as catalysts.

TABLE 1. SUMMARY OF DECOMPRESSION MODELS ~ continued

Model	Year	Concept	Details
		Tissular Bubble Models	
Van Liew[9]	1969	"clamping" phenomenon	The rapid equilibrium between the separated and the dissolved phases, slowing the tissue-to-blood gas exchanges, was possible for high bubble densities but became false for low to moderate bubble densities.
Yount[10]	1977	Varying Permeability Model. Recruitment of micronuclei populations	The number of bubbles formed for a given exposure was linked to the supersaturation level induced by the decompression. The model generated deep/short decompression stops as it limited the supersaturation levels to reduce the number of micronuclei recruited.
Vann[11]	1982	A physical threshold controlling the decompression rate	The desaturation kinetics of tissues during a compression was assumed either classical (perfusion) or instantaneous (diffusion) depending on the tissue tension and ambient pressure.
Hennessy and Hempleman[12]	1988	Instantaneous inert gas equilibrium	The volume of the formed bubble can be determined by tensions, ambient pressure and tissue volume. A bubble phase and an asymmetry between gas saturation and gas elimination kinetics were introduced.
Wienke[13]	1989	Reduced Gradient Bubble Model.	Workman's and Yount's works were merged. RGBM is a hybrid model that modifies a Haldanian model with factors to take some account of bubble mechanics to model gas phase production during decompression.
		Probabilistic Models	
Thalmann[14]	1984	Exponential-linear real-time-algorithm	Exponential-linear gas exchange kinetics and various matrices of maximum permissible tissue tensions; a slower tissue desaturation with linear gas exchange for inert gas elimination.
Gernhardt[15]	1991	Dynamics of microbubbles	A classical perfusion scheme was chosen for gas exchanges with additional parameters for tissue half-times: growth index for microbubbles, tissue bulk modulus, and initial radius of micronuclei.
Tikuisis[16]/Gault[17]	1994	Maximum likelihood method	Model parameters included surface tension, diffusion, solubility, and tissue half-times. The predicted maximum bubble radii in the compartments were compared to the predicted risks of Doppler bubble score database from a probabilistic model to establish a relationship.

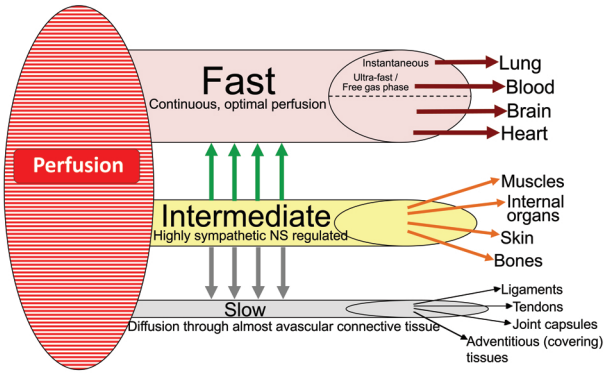
Model	Year	Concept	Details
		Vascular Bubble Models	
Hennessy's cardiac valve[18]	1989	Arterial bubble theory	Microbubble flow rate and global volume of microbubbles accumulated at the pulmonary filter constituted arterial bubble transfer. Proposed the basis of a global decompression model.
Flook[19]	1998	A classical perfusion-limited approach with 8 compartments	The volume of gas transported by by bubbles onto the pulmonary artery and central venous blood was calculated by a weighted mean of gas in bubbles in the venous drainage from each tissue.
Thom[20]	2011	Decompression stresses activate neutrophils causing vascular injuries	Increased circulating annexin V-coated microparticles derived from leukocytes, erythrocytes, platelets, and endothelial cells initiate decompression-induced neutrophil activation and vascular injuries.
		Endothelial Bubble Models	
Chappel and Payne[21]	2006	Formation of microbubbles at capillary endothelium level	The inert gas exchanges between the entrapped gas nuclei and the neighboring tissues as well as the dynamics of the resulting microbubbles growing until their release in the bloodstream were modeled.
Gutvik[22]	2009	Detectable venous gas emboli at the precordial level	The standard perfusion-limited tissue↔blood gas exchange formulation was modified to take into account the tissue↔bubbles gas exchange. The two selected compartments were for muscle and fat.

FIGURE 1. Quantifying ongassing and offgassing



LEGEND: Gradient, duration and gas mixture can be precisely calculated for a dive. Perfusion is the single component that cannot be accurately quantified.

FIGURE 2. Categories of perfusion



LEGEND: Perfusion can be divided into 3 categories. Each has distinct characteristics, mechanisms for regulation and flow/oxygen requirements.

Without a gradient (achieved with uncapping the bottle in the case of the carbonated beverage), physical dissolved gas will not escape the liquid phase.

Fourth, clinical presentations of DCS are a function of where in tissues the bubbles form in sufficient quantities and size to generate symptoms. Thus, DCS occurs as a result of overwhelming gradients and/or insufficient perfusion to offgas the supersaturated gases in tissues that result from ascending after a period of ongassing from breathing gases at increased ambient pressures. This paper offers an explanation as to why prediction of bubble formation remains imprecise, why tissue inert gas exchange is a function of tissue types, why DCS signs and symptom occur as they do and provides a rational guideline for return to diving after a DCS injury.

Components of ongassing and offgassing

Four main components determine the degree of ongassing and offgassing of the inert gas in the breathing medium with changes in ambient pressure (Figure 1). The four components are gradient, duration of exposure, gas mixture and perfusion. The gradient component is a direct function of the changes in ambient pressure and is explained by Henry's law. The duration of exposure is self-explanatory and measured by time. The longer the exposure to breathing the gas medium at the ambient pressure, the greater the changes in ongassing and offgassing. The gas mixture determines the amount of inert on- and offgassing according to Dalton's law. All three of these components are quantifiable and factored in to generate decompression tables and/or algorithms.

Unfortunately, the crucial component, perfusion, cannot be precisely determined for two reasons. First, there is an almost infinite variety of body tissues that require perfusion of varying degrees for their survival, function and repair. Secondly, and more importantly, except for a few critical tissues, perfusion may change more than 20-fold depending on the tissue demands [25]. The first reason is mitigated by disregarding the body tissue types and using a mathematical model of tissue half-times. This has merits since it can reflect perfusion and changes in perfusion (by switching from one tissue half-time to another) through a range of tissues. Contemporary algorithms use tissue half-times from almost instantaneous – i.e., free gas phase, to 500 minutes or more. The second reason is that changes in perfusion of non-critical tissues are so variable that no current mathematical model can account for all the permutations.

The variability of perfusion can be put into three categories (Figure 2).

Fast tissues – i.e., tissues with a rapid rate of saturation) – include the lung, blood, heart and brain. We label the lung and blood perfusion as ultra-fast tissues: ongassing and offgassing occur almost instantaneously with changes in ambient pressure. The heart and brain are the other two tissues of this category; all four are what we think conform to the tissues comprising Wienke's free gas phase designation. Their metabolism requires constant, uninterrupted perfusion, which is precisely regulated – primarily by the sympathetic nervous system. A moment's interruption of oxygen availability to the brain results in loss of consciousness,

TABLE 2. BLOOD VOLUME VS. POTENTIAL VOLUME OF THE CARDIOVASCULAR SYSTEM

Structure	Mechanism to increase volume	Factor	Comments
Heart	Increased filling	2.5-fold	Increased filling and/or rate
Arteries	Vasodilation	3-fold	Over 60,000 miles of end-to-end length; over 80% of length in capillaries. Through sympathetic nervous system control and chemical mediations, there is minimal flow through non-critical tissues at rest. If completely filled, it will require an enormous amount of blood.
Veins	Expansion	5-fold or more	
Capillaries	Filling	100-fold or more (estimate)	
Arteriovenous Shunting	Bypass capillary bed	10-fold (estimate)	Possible explanation for septic shock – i.e. blood & oxygen bypass capillary bed and no oxygen or nutrient exchange occur.
Sinusoids and Reservoirs (liver, spleen, bone marrow, erectile tissue)	Storage	3-fold (estimate)	Emptying of reservoirs significantly increase blood volume in hypovolemic shock

Note: The potential capacity of the vascular system is enormous. For example, looking at maximal fill of the heart, arteries, and veins adds up to an expansion factor of 10.5. At any one time, only 25% of the 60,000 miles of the capillaries are filled so there is, at a minimum, a 4-fold potential capacity for complete filling. The sinusoids and reservoirs add another 3-5 folds potential expansion of capacity (this information summarizes from Guyton and Hall's text, Reference 25).

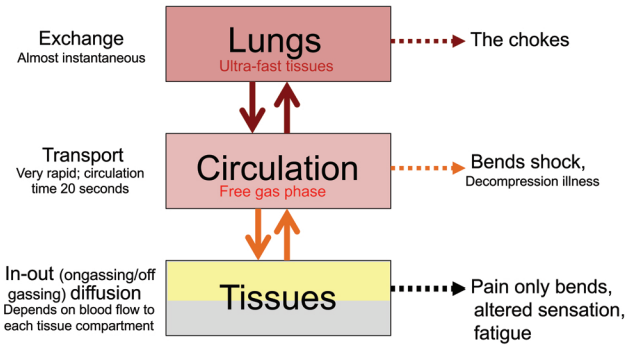
as seen in vasovagal syncope, chokeholds, third-degree heart blocks and Valsalva maneuvers after hyperventilation. The circulation time for the passage of blood from a vein through the heart and lungs to an artery is less than 20 seconds [24]. The brain requires a constant blood supply, which accounts for 20 percent of the cardiac output [25]. Any perturbation of offgassing because of abrupt changes in perfusion and/or gradients to these critical tissues when supersaturated with inert gas can have serious consequences.

The intermediate category of tissues with respect to inert gas ongassing and offgassing with changes in ambient pressure are those whose perfusions vary with their metabolic needs. They include muscles, visceral organs and gut, skin and subcutaneous tissues (especially with respect to wound healing) and bones. Their perfusion can vary 20-fold or more through changes in cardiac filling, cardiac output, vasodilatation, blood reservoirs, sinusoids and shunting (Table 2). With the human blood volume being approximately 5 liters and the vascular system's reserve capacities (i.e., their capacity to increase blood flow, dilate, fill with blood and/or store blood) being 20 liters or more, a careful regulatory system is essential in order to direct blood flow where it is needed.

The blood flow to the intermediate tissue is regulated by the sympathetic nervous system as well as chemical mediators, such as carbon dioxide and other products of metabolism. At rest, their perfusion is minimal, but it increases proportionally with metabolic activity. This reflects the "rob Peter to pay Paul" principle, where if two components of the intermediate category of tissues require maximal perfusion to meet their metabolic demands, one or the other may dysfunction. The limited blood volume for the intermediate category of tissues is directed to where it is most needed; the other tissues in this category may go with a blood supply that is inadequate to meet their metabolic needs.

When the intermediate tissues are inactive, their perfusion requirements are minimal. We believe this is why they rarely, if ever, show signs or symptoms of DCS because of their minimal ongassing and offgassing with changes in ambient pressure.

FIGURE 3. Target tissue categories for bends presentations



LEGEND: Signs and symptoms of DCS occur at the organ and tissue location where bubbles manifest themselves.

The slow category tissues are those that largely obtain their oxygen and metabolites indirectly by diffusion through almost avascular connective tissues. They include ligaments, tendons, joint capsules and adventitial tissues covering these tissues as well as those covering organs. Because of their avascularity they are predictably slow to ongas and offgas inert gases in response to changes in ambient pressures. These are the tissues more likely to demonstrate the signs and symptoms of pain-only DCS and neuropathies that do not conform to known peripheral nerve distributions or sensory/motor regions in the brain as will be demonstrated in Part 2 of this three-part series.*

The Gradient-Perfusion Model for explaining decompression sickness

With this fundamental anatomic and physiological information, it is logical to conclude that when perfusion is inadequate to offgas the supersaturated inert gas in the tissues and/or the gradients from decreases in ambient pressure are too great, autochthonous (in situ) bubbles form. Perfusion varies with tissue type, metabolic demands, hydration, medications, water temperature, and partial or complete occlusion of blood flow. Thus, when the supersaturated gas (or "silent" bubbles) overwhelms the ability for perfusion to carry the gas load to the lungs for exchange with the ambient breathing medium, DCS occurs. Our Gradient-Perfusion Model accounts for why symptoms appear as they do in DCS (Figure 3).

When gradients are most extreme, bubbles appear in the ultra-fast tissues of the lungs and cause a disorder known as "the chokes." When gradients overwhelm the transport of inert gas in the bloodstream, DCS "shock" and/or symptoms and signs of arterial gas embolism manifest themselves. This presentation has been labeled as decompression illness. With our GPM formulation, if bubbles form in the vasculature of the intermediate tissues, signs and symptoms of ischemia occur, such as cramping. Another manifestation is bubble formation in the adventitial tissues that causes pain by microscopic stretch of pain sensory structures and/or fatigue. Finally, if the supersaturation gradients are too great in the slow tissues, we postulate that they form bubbles in pressure-sensitive organelles in connective and adventitial tissues. These occurrences present as pain-only DCS, non-anatomical neuropathies or combinations of these signs.

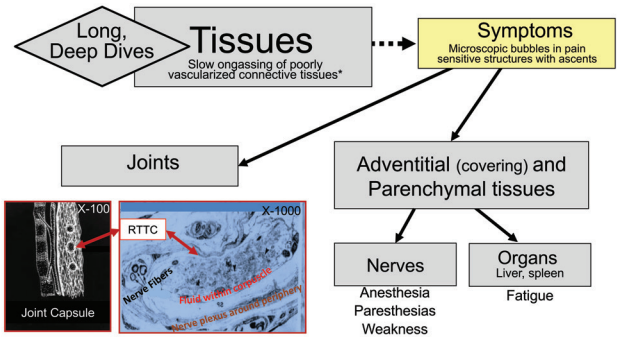
A histological explanation for pain-only DCS can be provided by the microscopic organelle, the Ruffini Type-2 corpuscle, a fluid-filled structure with a neuro-integrated capsule (Figure 4). This organelle is embedded in joint capsules and responds to stretch by signaling pain to the brain [26,27]. Ongassing to this sensory organelle by diffusion through the slow connective tissues of the joint capsule occurs during increases in ambient pressure. If decreases in ambient pressure generate gradients sufficient for bubbles to form within the organelle and thus distend or stretch the Ruffini Type-2 corpuscle, they will cause pain sensation in the joint without obvious evidence of bubble formation within the joint space or surrounding vasculature.

The Ruffini Type-2 corpuscle provides an explanation why a dislocated joint causes excruciating pain. Pain is presumed to occur due to distention of this organelle from stretching of the joint capsule. Yet, nearly complete relief results after the joint is reduced. This is explained by eliminating the distention of the organelle.

This organelle also provides a good model for explaining pain-only DCS. Pain-only DCS has no physical findings that have been identified at this point in time. Typically, symptoms occur after long, deep dives, even with slow ascents. This observation is consistent with pain-only DCS occurring in tissues with slow gas exchanges during changes in ambient pressure.

Pain in DCS is consistent with the microscopic Ruffini Type-2 corpuscle being distended by bubbles

FIGURE 4. Type I DCS – Pain-only, paresthesias



LEGEND: We postulate that micrscopic bubble formation in pain-sensitive structures such as the Ruffini Type-2 corpuscle (RTTC) and adventitial tissues provide an explanation for pain-only DCS as well as non-anatomical neuropathies and unxplained fatigue.

within its neuro-integrated capsule. With recompression – whether in air or oxygen – there is typically immediate, complete relief of pain symptoms in the joint. This conforms to our hypothesis that pain-only DCS is a mechanical problem and that with recompression, the bubbles in the Ruffini Type-2 corpuscle collapse, as explained by Boyle's law. This is consistent with the observation of the resolution of pain with reduction of dislocated joints.

Frequently, sensory and motor neuropathies in DCS do not conform to the neural innervations of the symptomatic structures. We believe this is explained by microscopic bubbles forming in the slow-to-ongas and -offgas adventitial tissues covering nerves. Regardless of how conflicting the neuroanatomy is with symptom presentations, these patients, in our experiences, nearly always have complete resolution of their symptoms with hyperbaric oxygen (HBO_2) recompression treatments. A corollary to this is the resolution of fatigue symptoms attributed to DCS with HBO_2 therapy. This presentation of DCS may be caused by microscopic bubbles, too small to be detected clinically, in the adventitial tissues surrounding visceral organs such as the liver and spleen or in the parenchyma, which disturbs their homeostasis.

DISCUSSION

It will never be possible to precisely quantify all the ramifications of perfusion. However, when a gradient for bubble formation is exceeded and/or perfusion is inadequate to transport and offgas the inert gas load through the lungs, the explanation as to why DCS and its symptoms and signs occurs becomes apparent. Once bubbles appear intravascularly or in tissues, two pathophysiological mechanisms may manifest themselves. These are mechanical stresses to the extent that there are interruptions of perfusion to tissues and/or the possible bubble endothelial reactions mentioned in the introduction. We feel the term "unexplained DCS" should be eschewed and the reason for disordered decompression sought when the cause of DCS such as violation of diving tables/computers did not occur. When the reason for disordered decompression is ascertained, appropriate management becomes apparent and logical advice can be provided as to whether the DCS victim should be given clearance to return to diving (Figure 5).

In more than 50 percent of DCS cases, dive table or computer violations are not apparent [28,29]. These are the situations where the Wienke Reduced Gradient Bubble Model and the Strauss Gradient-Perfusion Model (GPM) complement each other. Wienke's model provides an explanation of why bubbles occur and how to prevent them from becoming symptomatic. Our GPM accounts for the clinical presentations of DCS and the locations of bubbles that exceed physiological offgassing/offloading rates. Extreme gradients generate symptoms in the ultra-fast tissues (Figure 2). Inadequate perfusion, coupled with greater-than-physiologically tolerable gradients, is the source of bubbles in the intermediate and slow tissues. Signs and symptoms of DCS occur accordingly in the sites where the gradient-perfusion rates exceed the body's ability to offgas/offload the inert gas accumulated during exposure to increased ambient pressures.

Our Gradient-Perfusion Model provides guidance for return to diving (Figure 5). If a gradient problem is the cause – for example, due to omitted decompression – it is categorized as a "deserved" (or "expected) DCS "hit." A return to diving is satisfactory after a suitable rest period. In these situations, we recommend a minimum of two weeks in order to allow bubble-endothelial interactions to resolve. If the DCS hit is attributed to a perfusion problem, careful consideration is needed to make appropriate recommendations about returning to diving. This includes a cardiology consultation to rule out a patent foramen ovale or other aberrant connections

FIGURE 5. Return to diving after DCS

	deserved	disordered decompression
no residuals	yes after 2 weeks educate	no*
residuals (especially neurological)	no possible dive with special precautions	no

LEGEND: Four permutations provide guidance for return to diving after an episode of decompression.

***Note:** *if the bends victim is determined to dive again,* then: 1) cardiac consult (bubble study); 2) neurology consult (brain and spinal cord MR studies); and 3) trial of recompression (60 feet for 60 minues breathing air) are needed before a recommendation for return to diving is made. If cleared with the above, instructions in conservative diving practices (nitrox: depth and time limitations; number of dives per day, etc.) are given.

between the right and left side of the heart circulation, a neurology consultation to rule out nervous system pathology, and a controlled exposure to breathing air at 2 atmospheres absolute (66 feet/20 meters of seawater) for 60 minutes in a hyperbaric chamber.

CONCLUSIONS

In almost all unexplained cases of decompression sickness, the Gradient-Perfusion Model provides explanations as to why the signs and symptoms of DCS occurred; additionally, the GPM can explain why they occurred in the locations they do. The underlying pathophysiology is because gradients are too great and/or perfusion is inadequate to offgas/offload inert gas accumulation that occurs during increases in ambient pressure. Signs and symptoms occur as a consequence of the tissue type involved, whether it is a fast-, intermediate- or slow-to-saturate tissue.

We recommend not using the term "unexplained DCS" and, rather, seek the reasons that disordered decompression occurred. Whereas, the Wienke's Reduced Gradient Bubble Model as well as other bubble models try to predict why bubbles form in order to understand the cause and prevent DCS, our GPM supports the explanations for why DCS occurred and its clinical presentations. Secondary benefits from the GPM are that it can guide management and provide recom-mendations for a return to diving.

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Conflict of interest statement

The authors declare that no conflicts of interest exist with this submission.

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