Basic mechanisms of gas transport and past research using perfluorocarbons

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Perfluorocarbons, gas solubility, oxygen, nitrogen, carbon dioxide, nitric oxide, solubility, review article

Abstract

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Perfluorocarbon compounds have been utilized either in pure (neat) form or as emulsions suspended in aqueous fluids. These man-made chemicals possess a unique physical property allowing them to dissolve much more of the respired gases (oxygen, nitrogen and carbon dioxide) than any water-based system. Understanding the basic physical chemistry surrounding these emerging medical technologies will assure they are utilized to maximum benefit for mankind. It is clear they should not simply be viewed as 'blood substitutes' but rather as enhanced gas-transport pharmaceuticals.

Introduction

Carbon fluoride chemistry had its early beginnings in the 1930s–40s, during which time a unique feature of carbon halide bonds was discovered – a very high-energy ionic attachment. When a carbon chain or cyclic structure is completely substituted with halogens the ability of other carbon compounds to attack or change the parent structure is greatly limited.[1,2] They become, to a very great extent, inert and unable to be changed. The carbon-fluoride bond is unique in having the highest energy of any organic bond, 120 kcal·mole^{-1}. Solid perfluorocarbon (PFC) coatings are utilized to make non-stick pans. Liquid perfluorocarbon oils have other very useful properties.

During the Manhattan Project, it was discovered that such pure PFC oils were inert insulators. Uranium and plutonium could be stored safely in containers of PFC oils without fear of degradation and/or reaction. One would suppose unplanned reactions between uranium and plutonium could be a bad thing! A serendipitous observation occurred during such storage of radioactive material when it was noted that a tremendous amount of oxygen (O_2) dissolved in the oil. That observation went uninvestigated until the late 1960s and early 1970s, when a group of physiologists suggested that perhaps such oils could be used for medical purposes. LC Clarke, the famous physiologist and inventor of electrodes for pressure and biochemical measurements, along with Geyer and Galon, began experimenting with such PFC liquids.[1–4] They quickly found that tremendous amounts of dissolved O_2 and other respiratory gases could be harbored in equilibrium in such PFC oils. The now classic demonstration of rodents spontaneously breathing oxygenated PFC created outcries both of animal cruelty and fascination. Goldfish could swim in the water above the PFC and, as long as the PFC was in contact with 100% O_2, it seemed animals could live with liquid-PFC breathing for long periods, emerge and survive. This 'scientific trick' was picked up by Hollywood in the movie *The Abyss*. This was not just science fiction, as the producer had turned to advice from several excellent scientists such as Thomas Shaffer and Marla Wolfson, who were in liquid PFC-breathing research.[5–8] *The Abyss* did, however, spawn conjecture that perhaps such human liquid-PFC breathing could either be used as a way to escape from a disabled submarine or work as a new technology for deep sea exploration. Today, science fiction may be yet closer than we had previously believed.

Physiology of PFC usage

This article, however, is intended to discuss the physiology and physical chemistry whereby PFCs, either as pure oils or in intravenous emulsions, can enhance and change mammalian gas exchange.[9] The understanding of how these technologies work may well soon change medicine and mankind's future; but it is only through a careful understanding of their capabilities and limitations that science, not science fiction, will move them to technological reality.

Respiratory gases are transported both by active chemical binding and by passive solubility in fluids.[10] O_2 and CO_2 bind to haemoglobin as well as other metalloproteins throughout the body. The reactions are complex and widely reviewed elsewhere. What is important with regards to PFCs is the fact that, although erythrocytes carry vast amounts of O_2 within them, it is dissolved O_2 that ultimately fuels the energy production in target mitochondria. The red cells create a microenvironment of high-pressure O_2 immediately outside of their cellular membrane. Within Angstroms from their surface, the dissolved O_2 levels drop.[11] A popular myth exists that somehow cells pull O_2 from erythrocytes. It is rather that red cells, through biochemical changes in their cellular pH and 2,3 diphosphoglycerate (2,3-DPG), chloride ion, etc, release more O_2 thereby increasing dissolved O_2 in the local environment. The closer a red cell approaches the wall of a blood vessel the higher the local O_2 concentration gradient for cellular uptake. Total

Table 1
Oxygen content equations with and without perfluorocarbons present; note the dramatic increase in dissolved O_2 when PFC is present[9] (reproduced with permission with minor modification)

O_2 content equation	$Cao_2 = [1.36 \times Hb_{(conc)} \times Hb\ Sat] + [0.0031 \times PaO_2]$	Cao_2: total oxygen content; Hb_{conc}: haemoglobin concentration; Sat: saturation; Pao_2: arterial partial pressure of oxygen
O_2 content equation with PFC present	$Cao_2 = [1.36 \times Hb_{(conc)} \times Hb\ Sat] + (0.0031 \times PaO_2) + (0.1432 \times PaO_2 \times \beta)$	β: Fluorocrit (percentage of whole blood taken up by PFC particles – Oxycyte)
O_2 content equation done a different way with a second-generation PFC – Perflubron	O_2 blood $= (Y \times O_{2max}) + (4.7 \times 10^{-3} \times V_{RBC} \times P) + (2.9 \times 10^{-3} \times V_{plasma} \times P)$	Y: relative saturation of Hb; O_{2max}:. maximum O_2-carrying capacity of Hb (100% saturation; ml O_2.100 ml^{-1} blood) and equals 0.45 × %haematocrit; V_{RBC}: fractional volume of the red blood cell; V_{plasma}: fractional volume of the plasma; P: total ambient pressure. A 1 g.PFC per kg BW dose added to the blood produces a 30% increase in total O_2 in the blood (all present and available for metabolism, since it is dependent only on Henry's law)
Gradient of O_2 from an erythrocyte (Hb) to the mitochondria	$VO_2 - DO_2\ (PcO_2 - PmitO_2)$	VO_2: O_2 uptake; DO_2: O_2 diffusing capacity; PcO_2: average capillary partial pressure O_2; $PmitO_2$: average mitochondrial partial pressure O_2

O_2-carrying capacity can be calculated from a standard equation (Table 1).[9] That equation takes into account, but downplays, dissolved O_2 in plasma. Indeed, in most medical teaching the content of dissolved O_2 is disregarded, yet it is dissolved O_2 that the mitochondria actually utilize. Therefore, erythrocytes function as a bank of stored O_2 that continuously overpressurizes the aqueous plasma fluid such that the net flow of O_2 is to the mitochondria of metabolizing cells. As blood courses through tissues, it exchanges O_2 between venous and arterial blood, as well as driving it into tissues. The levels of various gases within tissues is noted in Table 2.[12] The plasma not only is a conduit for gas movement but a resistor, as its capacity for gas solubility is quite limited (Figure 1).[13]

Understanding that the plasma gap functions as a resistor brings to light how PFCs may well be utilized for the future.[13] First, one has to understand the physics of gas solubility in PFCs. 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 equilibrium with that liquid*."[9] Every fluid has an inherent solubility coefficient for every gas, dependent upon relative molecular polarity and molecular size. Water is a highly polar molecule, whereas lipids tend to be considerably less polar. Most fats, however, still have a large number of protons (hydrogen atoms) as side chains and, therefore, are relatively polar. Once a hydrocarbon molecule has all its available valences substituted with halogens (preferably fluoride), then the resultant carbon-based oil becomes highly non-polar. PFC gas solubility is noted in Table 3.[14]

Pure PFC can carry large amounts of O_2 dissolved at 101.3 kPa.[14] Even more soluble than O_2 is carbon dioxide (CO_2), and nitrogen (N_2) is somewhat less soluble in PFC than is O_2. However, N_2 is highly insoluble in water. Remember the O_2 solubility in plasma is 0.0031 ml·100ml^{-1}, whereas for a PFC emulsion (not pure PFC) the solubility of O_2 is 50-fold higher (Table 1). These facts can be utilized in making gas solubility and content equations (Table 1).

Figure 1
Representation of a tissue bore with a capillary running through it; the cylinders inside the capillary represent red blood cells separated by plasma gaps; various resistances to O_2 movement are indicated, with corresponding PO_2 within the plasma, vessel wall and tissue[13] (adapted with permission)

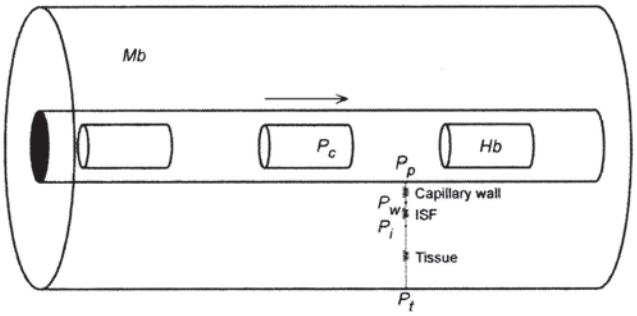


Table 2
Gas partial pressures in various parts of the human body; note the low tissue PO_2 and that all tissues are saturated with N_2 at sea level

Sample site	O_2	CO_2	N_2	H_2O	Total
Inspired air	158	0.3	596	5.7	760
Expired air	116	32	565	47	760
Alveolar air	100	40	573	47	760
Arterial air	100	40	573	47	760
Venous blood	40	46	573	47	706
Tissues	≤30	≥50	573	47	700

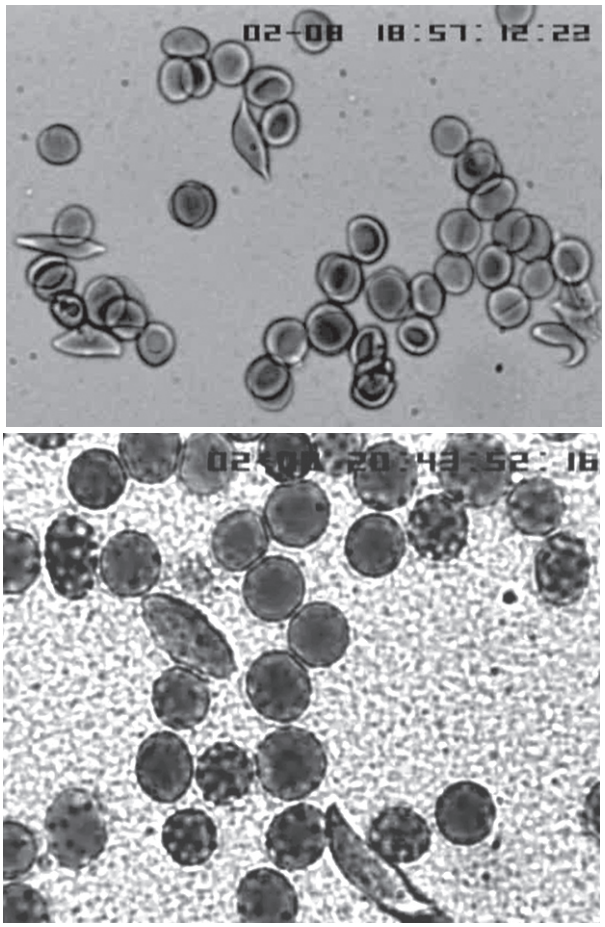
Table 3
O_2 solubility at 101.3 kPa in different pure perfluorocarbons; note that these PFC emulsions are between 20–60% PFC whereas modern emulsions are 40–60% PFC; one is limited in usage of the products to approximately 2–5% fluorocrit[9]

Compound	Solubility ($mlO_2 \cdot 100ml^{-1}$ of compound)
Perfluorodihexyl ether	55.42
Perfluorodibutyl sulfur tetrafluoride	48.02
Perfluorotriisobutylamine	44.37
Perfluoro-(*N*-ethylmorpholine)	50.10
Perfluoro-*N*,*N*-dipropylmethylamine	52.60
Perfluorotriethylamine	53.86
Perfluoro-*N*-methylpiperidine	41.33
Perfluoro-*N*-methylmorpholine	37.57
Perfluoro-*N*,*N*-dimethyl-*N*-hexylamine	51.51
Perfluoro-*N*-butylmorpholine	50.59
Perfluoro-4-(*N*,*N*-dimethyl-2-aminoethyl)-morpholine	45.07
F-Tertbutylperfluorocyclohexane	43.00

Pure PFC has been utilized to enhance O_2 delivery in the lungs.[5–8] Small amounts have been nebulized, causing a coating of PFC in the alveoli and terminal bronchi. These experiments seemed to use the PFC as a surfactant, although the enhanced O_2 solubility may have enhanced gas delivery. Also, fully filling the tracheo-bronchial tree with pure PFC and creating liquid-PFC breathing has been accomplished in both animal and human studies. This works to enhance gas transport, and data from respiratory distress syndromes suggest that it may have a clinical application there in the future. Some studies have suggested that by using liquid-PFC breathing, possibly in conjunction with intravenous PFC, decompression sickness could be averted.

Most PFC utilizations in commercial development have focused upon intravenous emulsion technology.[9] PFC, an oil, is immiscible with plasma, therefore, micro-particles of fat emulsions (micelles) have been created.[15–17] At least one technology utilizes perfluorododecapentane, which has a boiling point close to body temperature.[18] This is injected in liquid form and flashes instantly into micro-gas particles, leading to enhanced gas transport within the particles. However, the rest of this article will focus upon the biophysics and chemistry of the emulsions in preparation today.[19–21] Modern-day emulsions are made from egg yolk phospholipids, quite similar to propofol and intralipid. The particles closely range around 0.2 microns in diameter, in comparison to an erythrocyte which is 5–8 microns. The micelles are considerably denser than other formed elements of the blood, and they will separate out in low-flow or standing fluids. However, with normal blood flow the PFC micelles are dispersed between red cells and also pushed to the walls of the blood vessels. The plasma gap essentially is replaced with micelles forming a gas-conduit bridge from

Figure 2
Human sickle red cells in an artificial capillary; A: normal plasma, B: PFC has been added; note the granular appearance of the PFC micelles. The dramatically increased solubility of O_2 in these micro particles overcomes the resistance of the plasma gap when PFC is added to whole blood[9] (reproduced with permission)



red cells to endothelium and vice versa (Figures 1 and 2). If one considers that the solubility of respiratory gases is up to 50 times higher than in plasma, then this bridge of microparticles allows for rapid gas transfer. Diffusion speed appears to be enhanced by PFC micelle presence, but in reality it is simply a function of enhanced solubility of gas within each micelle and the close proximity of each micelle that makes gas movement appear to speed up.[9]

Because gas molecules in PFC micelles are not chemically bound but are held through enhanced solubility, every molecule of O_2 is available for metabolic utilization. In whole blood, haemoglobin has a complex interaction between each added O_2 molecule in the four haem moieties, as well as being modulated by pH, chloride ion, and 2,3–DPG. Therefore, under normal physiologic conditions, the maximum 21 volumes per cent of O_2-carrying capacity can only release from haemoglobin approximately 5–6 volumes per cent of O_2 (tissue demand). PFC micelles are

rapidly in equilibrium with any microenvironment they inhabit. It is gas solubility according to Henry's Law and the relative gas partial pressures in those tissue/blood or lung microenvironments that determine the content of gases dissolved within them at any one time. PFC can be effective as a third compartment of gas-carrying capacity within the blood stream. The amount of added potential gas-carrying capacity can be calculated (Table 1).

However, gas delivery from the red cells should be thought of as the most important physiologic contribution of PFC. Using normal and low haematocrit blood, adding PFC emulsions increases the mass transfer coefficient by 14% or more. Convective gas movement (forward propulsion of blood) and diffusive gas movement are considerably different.[13] With normal whole blood, convective movement must be present, otherwise tissues become hypoxic very quickly and withdraw all available O_2 from the microcirculation. In several recent studies, it has been shown that, with PFC present in the microcirculation at low or no-flow convective states, tissue O_2 delivery remains present. This must be due to the massively enhanced diffusion effects.

O_2 diffusion is important for normal metabolic function. The first generation PFC that garnered approval for treatment of myocardial ischaemia during balloon angioplasty was not easy to use commercially and was withdrawn from the market. Today, a third-generation compound, (Oxycyte™, Oxygen Biotherapeutics Inc, USA) is being tested for a wide range of tissue ischaemia indications, including traumatic brain and spinal cord injury, organ preservation, carbon monoxide poisoning and cardiopulmonary resuscitation.

N_2 is highly insoluble in whole blood and tissue. Rapid changes in ambient pressure can cause supersaturation leading to formation of a gas phase in blood and tissues. PFC has been shown to increase xenon (another highly insoluble gas) movement out of striated muscle by well over 100%. In multiple experiments using PFC infusions, air embolism effects have been reduced.[17,20,22–30] These studies show dramatic reductions in organ effects. The speed of bubble resolution has been shown to be increased by PFC presence, but the entire story is not simply the increased solubility of N_2 in PFC.[30] Bubbles sticking and interacting with endothelial cells are decreased, perhaps by the surfactant effects of the PFC as well as its emulsifiers. PFC also has under-investigated, independent anti-inflammatory effects and may preserve endothelial cell function. It is entirely possible that PFC may change the stress induced upon endothelial cells when a bubble is present in the microcirculation and that the glycocalyx itself is better preserved.[31] Whilst PFCs speed up the dissolving of N_2, perhaps the more important effect is on O_2 delivery to tissues that would otherwise become hypoxic from the blood vessel blockade due to bubble formation.

CO_2 is far more soluble in PFC than in either whole blood or plasma, and, when PFC is present, cerebral blood flow increases, perhaps 10% or more. Whether this is due to fluxes in CO_2 or whether other mechanisms are at play is not established.[9] Either way, in models of neurologic ischaemia, traumatic brain and spinal cord injury and stroke, PFC appears to have a unique neurological protective effect.

Another important gas in the microcirculation is nitric oxide (NO). NO exerts so many different cellular function-controlling events that it is hard to generalize everything it does. NO is probably very highly soluble in PFC micelles. Only a small number of studies to date have looked at NO effects in the presence of PFC. It appears that PFC at first works as a NO sink, but once it is equilibrated, it then may act as a NO donor.[32] To date, no one has tried attaching NO donors within the micelle itself or pre-equilibrating the emulsions with NO before infusion. Just as PFC micelles enhance movement of O_2 from erythrocytes, so might such micelles enhance the movement of NO from endothelial cells to erythrocytes. Normally haemoglobin is a NO binder and, being encased in the red cells streaming through the centre of capillaries, it is held away from endothelial cells. If PFC enhances NO movement from endothelial cells to haem proteins, one might expect to see hypertension, but this is not described as a side effect of PFC infusions.

Conclusion

In the future, it is likely that an intravenous PFC will become approved as a treatment for tissue ischaemia. Today, a phase IIb double-blind, placebo-controlled, large (128 patients), dose-escalation trial of PFC for the treatment of civilian closed-head injury is underway. Animal studies in blast-induced traumatic brain injury are showing efficacy, and that programme is expanding quickly due to its military importance. The use of PFC infusions for sickle cell crisis and carbon monoxide poisoning is being researched as are other indications. In a second article, the use of PFCs for decompression illness will be reviewed. Suffice it to say that success in such a treatment is dependent upon understanding of the physico-chemical means by which PFC emulsions can carry both O_2 and N_2. The future investigation of enhanced delivery/removal of respiratory gases by PFC will almost certainly encompass a more basic understanding of the physiology of CO_2 and NO fluxes when PFC is present. To look way into the future, the use of liquid-inhaled PFC may yet find a medical usage. It does offer the possibility of being used as a method to create or enhance suspended animation as well as for individual organ preservation.[33] Work and discussions are on-going with space agencies to understand how this might be possible.[34] PFC as a tool for medical application, temporarily changing the way that respiratory gases are transferred within the body, is very exciting.

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References

1 Clark LC. Emulsion of perfluoronated solvents for intravenous gas transport. *Fed Proc*. 1981;34;1468-77.

2 Clark LC, Becattini K, Kaplan S. The physiological effects of artificial blood made from inert organic solvents. *Ala J Med Sci*. 1972;9:16-29.

3 Geyer RP. Substitutes for blood and its components. *Prog Clin Biol R*es. 1978;19:1-26.

4 Geyer RP. "Bloodless" rats through the use of artificial blood substitutes. *Fed Proc*. 1975;34:1499-505.

5 Wolfson MR, Shaffer TH. Pulmonary applications of perfluorochemical liquids, ventilation and beyond. *Paediatr Respir Rev*. 2005;6:117-27.

6 Jeng MJ, Yang SS, Wolfson MR, Shaffer TH. Perfluorochemical (PFC) combinations for acute lung injury: an in vitro and in vivo study in juvenile rabbits. *Pediatr Res*. 2003;53:81-8.

7 Nakstad B, Wolfson MR, Shaffer TH, Kähler H, Lindemann R, Fugelseth D, et al. Perfluorocarbon liquids modulate cell-mediated inflammatory responses. *Crit Care Med*. 2001;29:1731-7.

8 Greenspan JS, Wolfson MR, Shaffer TH. Liquid ventilation: clinical experiences. *Biomed Instrum Technol*. 1999;33:253-9.

9 Spiess BD. Perfluorocarbon emulsions as a promising technology: a review of tissue vascular gas dynamics. *J Appl Physiol*. 2009;106:1444-52.

10 Ward KR, Torres Filho I. Oxygen transport monitoring: the basis for developing transfusion triggers. In: Spiess BD, Spence R, Shander A, editors. *Perioperative transfusion medicine*. Baltimore, MD: Lippincott, Williams and Wilkins; 2006. p. 55-66.

11 Homer LD, Weathersby PK, Kieslow LA. Oxygen gradients between red cells in the microcirculation. *Microvasc Res*. 1981;22:308-23.

12 Wardley-Smith B, Hadley MJ. Recent molecular theories of general anaesthesia. *Br J Anaesth*. 1979;51:619-26.

13 Eggleton CD, Tuhin KR, Popel AS. Predictions of capillary transport in the presence of fluorocarbon additives. *Am J Physiol Heart Circ Physiol*. 1998;275:H2250-7.

14 Geyer RP. Substitutes for blood and its components. *Prog Clin Biol Res*. 1978;19:1-26.

15 Tremper KK, Friedman AE, Levine EM, Lapin R, Camarillo D. The preoperative treatment of severely anemic patients with a perfluorochemical oxygen-transport fluid. Fluosol DA. *N Engl J Med*. 1982;307:277-83.

16 Spahn DR, Waschke KF, Standl T, Motsch J, Van Huynegem L, Welte M, et al. Use of perflubron emulsion to decrease allogeneic blood transfusion in high-blood-loss non-cardiac surgery: results of a European phase 3 study. *Anesthesiology*. 2002;97:1338-49.

17 Cochran RP, Kunzelman KS, Vocelka CR Akimoto H, Thomas R, Soltow LO, et al. Perfluorocarbon emulsion in cardiopulmonary bypass prime reduces neurologic injury. *Ann Thorac Surg*. 1997;63:1326-32.

18 Lundgren C, Bergoe G, Olszowka A, Tyssebotn I. Tissue nitrogen elimination in oxygen-breathing pigs is enhanced by fluorocarbon-derived intravascular microbubbles [Abstract]. *Undersea Hyperb Med*. 2005;32:215-6.

19 Zhu J, Hullett JB, Someras L, Barbee RW, Ward KR, Berger BE, et al. Intravenous perfluorocarbon emulsion increases nitrogen washout after venous gas emboli in rabbits. *Undersea Hyperb Med*. 2007;34:7-20.

20 Kwon TH, Sun D, Daugherty WP, Spiess BD, Bullock MR. Effect of perfluorocarbons on brain oxygenation and ischemic damage in an acute subdural hematoma model in rats. *J Neurosurg*. 2005;103:724-30.

21 Daugherty WP, Levasseur JE, Sun D, Spiess BD, Bullock MR. Perfluorocarbon emulsion improves cerebral oxygenation and mitochondrial function after fluid percussion brain injury in rats. *Neurosurgery*. 2004;l54:1223-30.

22 Spiess BD, Zhu J, Pierce B, Weis R, Berger BE, Reses J, et al. Effects of perfluorocarbon infusion in an anesthetized swine decompression model. *J Surg Res*. 2009;153:83-94.

23 Spiess BD, McCarthy RJ, Tuman K, Tool K, Woronowicz A, Ivankovich AD. Treatment of decompression sickness with a perfluorocarbon emulsion. *Undersea Biomed Res*. 1988;15:31-7.

24 Spiess BD, Tuman K, McCarthy R, Ivankovich AD. Protection from coronary air embolism by a fluorocarbon emulsion (FC-43) in dogs. *J Cardiothorac Anest*. 1987;1:210-5.

25 Spiess BD, Braverman B, Woronowicz A, Ivankovich AD. Protection from cerebral air emboli with perfluorocarbons in rabbits. *Stroke*. 1986;17:1146-9.

26 Tuman K, Spiess BD, McCarthy R, Ivankovich AD. Cardiorespiratory effects of venous air embolism in dogs receiving a perfluorocarbon emulsion. *J Neurosurg*. 1986;65:238-44.

27 Spiess BD, McCarthy R, Piotrowski D, Ivankovich AD. Protection from venous air embolism with fluorocarbon emulsion FC-43. *J Surg Res*. 1986;41:439-44.

28 Herren JI, Kunzelman KS, Vocelka C, Cochran RP, Spiess BD. Horseradish peroxidase as a histological indicator of mechanisms of porcine retinal vascular damage and protection with perfluorocarbons after massive air embolism. *Stroke*. 1997;28:2025-30.

29 Herren JI, Kunzelman KS, Vocelka C, Cochran RP, Spiess BD. Angiographic and histological evaluation of porcine retinal vascular damage and protection with perfluorocarbon after massive air embolism. *Stroke*. 1998;29:2396-403.

30 Eckmann DM, Lomivrotiv VN. Microvascular gas embolization clearance following perfluorocarbon administration. *J Appl Physiol*. 2003;94:860-8.

31 Eckmann DM, Armstead SC. Influence of endothelial glycocalyx degradation and surfactants on air embolism adhesion. *Anesthesiology*. 2006;101:1220-7.

32 Rafinkova O, Sokolova E, Rafikov R, Nudler E. Control of plasma nitric oxide bioactivity by perfluorocarbons; physiological mechanisms and clinical implications. *Circulation*. 2004;110:3573-80.

33 Spiess BD. The potential role of perfluorocarbon emulsions in decompression sickness. *Diving and Hyperbaric Medicine*. 2010;40:(28-33).

34 Eckmann DM, Zhang J, Lampe J, Ayyaswang PS. Gas embolism and surfactant-based intervention: implications for long-duration space based activity. *Ann NY Acad Sci*. 2006;1077:256-69.

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The potential role of perfluorocarbon emulsions in decompression illness

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Abstract

(Spiess BD. The potential role of perfluorocarbon emulsions in decompression illness. *Diving and Hyperbaric Medicine*. 2010;40:28-33.)
Decompression illness (DCI) is an occasional occurrence in sport, professional, and military diving as well as a potential catastrophe in high-altitude flight, space exploration, mining, and caisson bridge construction. DCI theoretically could be a success-limiting problem in escape from a disabled submarine. Perfluorocarbon emulsions (PFCs) have previously been investigated as 'blood substitutes' with one approved by the United States Food and Drug Administration for the treatment of myocardial ischaemia. PFCs possess enhanced (as compared to plasma) respiratory gas solubility characteristics, including oxygen, nitrogen and carbon dioxide. This review examines approximately 30 years of research regarding the utilization of PFCs in gas embolism as well as experimental DCI. To date, no humans have been treated with PFCs for DCI.

Introduction

Decompression illness (DCI) is an incompletely defined clinicopathological diagnosis in humans with a wide spectrum of presenting signs and symptoms.[1,2] The disease is caused by gas bubble formation/movement in tissues and within the vascular tree or by gas forced into the circulation from pulmonary barotrauma. These gas bubbles cause either primary direct tissue destruction or secondary events from decreased blood flow (oxygen delivery), endothelial cell dysfunction, inflammation, coagulopathy/thrombosis and many other effects. The readership is familiar with many of the manifestations and difficulties with the diagnosis of DCI and is referred elsewhere for review.[1–3]

Mankind lives and works most often in a narrow range of ambient gas pressures. The gas column above us functions as a fluid, exerting continuous equal pressure to all parts of the body. Gases are soluble in tissues and blood, based upon Henry's law. At 101.3 kPa (1 bar) the human body is saturated, with all respiratory gases in equilibrium with the partial pressures of each gas. Seventy per cent of the body is made up of water, therefore the relative solubility coefficients for respiratory gases in water versus fat (oils) determine the total amount of gas dissolved in aqueous media or tissues at any one time.[4,5] It is through a sudden decrease in ambient pressure that tissues and blood potentially become supersaturated with gases. Supersaturation leads to bubble formation. The respiratory gases leave their dissolved state when some, as yet undefined, parameter allows for a small nidus of micro-bubble formation to occur.[6] It has been suspected that micro-particles allow for the original formation of micro-bubbles.[6] Once formed the micro-bubbles grow, potentially rapidly, as local, supersaturated gases move from tissue and blood into the gaseous phase of the micro-bubble.

Growth of a bubble is dependent upon gas composition, internal/external pressures and the surface tension of the bubble itself.[6] Bubble dynamics is an entire study unto itself, but, suffice to say, particularly within the blood stream, bubbles are rapidly coated with proteins that themselves then have complex interactions with tissues, cells and the micro-environment.[6–7] DCI is often thought to be a disease of diving, with inadequate times for gas equilibration between various faster and slower equilibrating tissue categories. However, any rapid reduction in ambient pressure may cause DCI and as man ventures into ever more unique