THE RELATIONSHIP OF INERT GAS AND VENOUS GAS EMBOLI

TO DECOMPRESSION SICKNESS

by

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A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science
in the Department of Mechanical Engineering and Materials Science
in the Gradate School of
Duke University

2003

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DCS	Decompression sickness
$T_{1/2}$	Tissue halftime (min)
P_vN_2	Venous blood nitrogen partial pressure (tension) (atm)
P_tN_2	Tissue nitrogen partial pressure (tension) (atm)
P_aN_2	Alveolar nitrogen partial pressure (tension) (atm)
_$_b$	Inert gas solubility in blood
_$_t$	Inert gas solubility in tissue
Q	Rate of blood flow (ml/min)
V_t	Volume of tissue (ml)
Q_{vt}	Rate of blood flow per tissue volume (perfusion) (ml/min/100ml)
k	Blood-tissue gas exchange constant
fsw	Feet sea water
VGE	Venous gas emboli
KM	Kisman-Masurel, scoring system for Doppler detected VGE
HBG	High bubble grade, Spencer score >2
NEDU	Navy Experimental Diving Unit
ATA	Atmospheres absolute
PO_2	Partial pressure of oxygen (atm)
DCS I	Type I DCS
DCS II	Type II DCS
LEM	Multi-gas linear exponential model
cPDCS	Conditional probability of DCS

cP	Another abbreviation for cPDCS used in Figures and Tables
D1	Dive depth (ft)
T1	Dive time, corresponds to time spent at D1 (min)
TDT	Total decompression time, time spent returning from D1 to surface (min)
PrT	Derived term from Hempleman concept, dive depth multiplied by square root of bottom time
BMI	Body mass index
_	Constant coefficients of variables in logistic regression equation (6)
OR	Odds ratio
k_{N2}	Baseline k for a diver at rest breathing nitrogen-oxygen
c_{ex}	Constant multiplier of k to account for effects of exercise at depth
chn	Ratio of partition coefficients for helium and nitrogen, multiplies k to account use of helium as the diluent gas
Pt	Derived tissue tension obtained from “physiological” model

1 Introduction

Decompression sickness, or “the bends”, results from a reduction in ambient pressure and is a hazard for workers in hyperbaric and hypobaric environments. Decompression sickness (DCS) obtained the nickname “the bends” from its occurrence in caisson workers during the construction of the Eads Bridge in St. Louis (McCullough, 1972). Caisson workers would enter a pressurized caisson at the surface and descend to the foundation to dig into the river muck until they reached bedrock. Upon returning to normal atmospheric pressure (surfacing), many workers would walk as if they were wearing a corset fashionable at the time called the Grecian bend, hence the nickname “the bends.”

Gas bubbles, largely of inert gas, are believed to cause DCS, although the exact mechanisms are not completely understood. Procedures to prevent decompression sickness involve slowing ascent according to a specified depth/time profile known as a decompression schedule. Most current schedules consist of progressively longer pauses in ascent, called decompression stops, as the diver gets shallower. The efficacy of these procedures is not perfect, because some divers still suffer from DCS. Decompression sickness generally involves symptoms of limb pain but serious symptoms can include numbness, nausea, weakness, paralysis, and even death. The best treatment for DCS is recompression with the administration of 100% oxygen.

1.1 Haldane Theory

Paul Bert, a French physiologist, identified the cause of decompression sickness as gas bubbles in 1878 (Bert, 1878). Bert deduced that breathing air under pressure caused increased nitrogen in the lungs to dissolve in the blood and tissues in accordance with Dalton's law of partial pressures. Bert discovered that if the pressure were reduced too quickly, bubbles would form as the nitrogen came out of solution when blood and tissue became supersaturated with respect to the environment (Tikuisis and Gerth, 2003). Serious DCS in animals and humans appeared to be clearly caused by bubbles, but it was more difficult to find direct evidence of bubbles for mild symptoms.

J. S. Haldane, an English physiologist, developed and tested the theory of stage decompression in 1905-1907. Haldane postulated that during a dive, dissolved nitrogen entered or left the tissue in the circulating blood until the tissue equilibrated with the environmental partial pressure. He assumed that the arterial blood inert gas concentration equilibrated instantaneously with that of the tissue so the concentration of gas was uniform throughout, and therefore the tissue could be considered well stirred (Tikuisis and Gerth, 2003).

Haldane postulated that the absorption rate of dissolved nitrogen would change from fast to slow as the tissue tension approached the alveolar partial pressure. To describe this diminishing absorption rate, he defined a tissue halftime ($T_{1/2}$) as the time it would take to halve the difference between the tissue tension and alveolar partial pressure. After six halftimes, the tissue tension equals 98% of the alveolar partial pressure and the tissue is considered saturated.

Haldane used five halftimes of 5, 10, 20, 40, and 75 minutes to represent the different perfusion rates of body tissues. He postulated that DCS would not occur if bubbles did not form and theorized that no bubbles would form during decompression if the ratio of the dissolved nitrogen tension in tissue to the surrounding absolute pressure did not exceed a critical value of 2:1 (Boycott et al., 1908).

Haldane proposed a method of stage decompression that would prevent the dissolved nitrogen tension in any tissue from exceeding the critical 2:1 ratio. Stage decompression operates by tracking the nitrogen tension in each tissue, and if the 2:1 ratio is in danger of being exceeded, the diver stops ascending until sufficient nitrogen is eliminated to allow safe ascent to the next stage. At the beginning of decompression, the tissues with shorter halftimes control the decompression stages (or stops) because they have taken up more inert gas. However, as the decompression progresses, the controlling tissues change to those with longer halftimes because those with shorter halftimes off gas more quickly.

1.2 Well-stirred (Perfusion Limited) Tissue

Subsequent workers have derived a more quantitative description of inert gas exchange in a well-stirred tissue (Kety, 1951). It is useful to review this derivation below. First, the venous (P_vN_2) and tissue (P_tN_2) nitrogen tensions are assumed equal to represent rapid diffusion between closely spaced capillaries. Figure 1 demonstrates the mass balance for nitrogen,

$$(N_2)_{stored} = (N_2)_{in} - (N_2)_{out}.$$

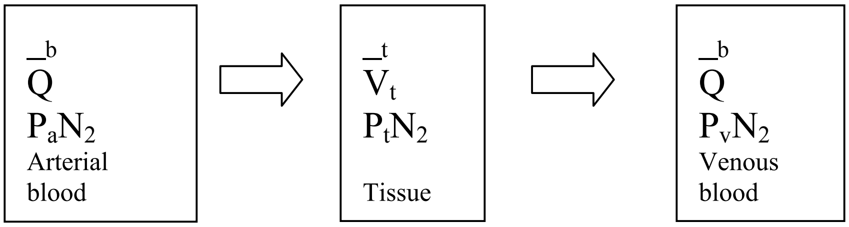

Figure 0: Illustration of the nitrogen mass balance in a perfusion-limited tissue.

Nitrogen enters the tissue with the arterial blood at a tension equal to the alveolar partial pressure (P_aN_2) and leaves with the venous blood where Q, _$_b$, and _$_t$ are defined as the rate of blood flow (Q, ml/min), the gas solubility in blood (_$_b$, ml gas/ml blood/atm), and the gas solubility in tissue (_$_t$, ml gas/ml tissue/atm). V_t is the tissue volume in milliliters. The rate of change of P_tN_2 defines the rate at which nitrogen is stored in the tissue. Thus,

and $$\frac{dP_t}{dt} + k \cdot P_t = k \cdot P_a \qquad (1)$$

where *k* is the blood-tissue gas exchange time constant. The solution to equation (1) is

$$P_t(t) = P_a\left[1 - e^{(-k \cdot t)}\right] + P_0 e^{(-k \cdot t)} \qquad (2)$$

where P_0 is the initial N_2 tension. This solution allows the inert gas tension in tissue to be calculated throughout any given dive profile. It is a convenient mathematical simulation of inert gas exchange but not necessarily complete.

The blood-tissue gas exchange time constant, *k*, controls the rate of inert gas exchange in the tissue and depends upon Q, _$_b$, and _$_t$. The expression for *k* is given by

$$k = \frac{\alpha_b \cdot Q_{vt}}{100 \cdot \alpha_t} \qquad (3)$$

where $Q_{vt} = \dfrac{Q}{V_t}$ is known as perfusion, often expressed as ml blood/min/100ml tissue.

The ratio of inert gas solubility in blood to that in tissue is known as the partition coefficient. The rate of gas uptake by the tissue is fast for a large *k* and slow for a small *k*. The tissue halftime, $T_{1/2}$, depends on *k* and can be expressed as

$$T_{1/2} = \frac{0.693}{k} \qquad (4)$$

Therefore, tissues with short halftimes have a large *k* and exchange gas rapidly; conversely, tissues with long halftimes have a small *k* and exchange gas more slowly.

It can be seen from (3) that conditions affecting perfusion, such as exercise and immersion, change the rate of inert gas exchange. Exercise increased the rate of inert gas uptake for both divers at sea level (Behnke and Willmon, 1941) and divers at depth compared to resting divers (Dick et al., 1984). Some typical values for perfusion are shown in Table 1. Equation (3) also shows that inert gases with different solubilities would possess different halftimes.

Tissue	Perfusion (ml/min/100ml)
Muscle (rest)	2-5
Muscle (exercise)	50-75
Brain (gray matter-maximal dilatation)	300-400
Brain (gray matter)	100
Brain (white matter)	20-25
Skin (cold)	2-3
Skin (warm)	40-60

Table 0: Empirically derived values for perfusion in different tissues under various conditions (Folkow and Neil, 1971).

1.3 Effects of Bubbles on Inert Gas Exchange

Most current decompression models are based on the Haldane theory and assume no bubbles form in tissue (Hamilton and Thalmann, 2003). The presence of bubbles in tissue slows the rate of gas elimination because the gas must first diffuse from the bubble back into the tissue before it can be transported to the lung for removal (Vann, 2003 chapter 4). When a bubble is present in the tissue, exponential Haldane gas exchange kinetics no longer apply, and inert gas washout becomes linear instead of exponential.

To remedy the failure of Haldane models to safely project limits for longer and deeper dives, Thalmann introduced the assumption that excess supersaturation in tissue during decompression caused inert gas exchange to shift from the faster exponential kinetics to slower linear kinetics (Thalmann 1981, 1983). Linear kinetics persisted until the supersaturation was gone. Thalmann called this the Linear-Exponential (LE) model. The LE model was used in both NEDU 1-85 and NEDU 8-85 to develop the decompression tables for helium and nitrogen that are analyzed in this thesis.

1.4 Deterministic Decompression Models

The Haldane decompression model considered a decompression to be ‘safe’ if the critical ratio was not violated during ascent and ‘unsafe’ if it was violated. This is known as a deterministic model, in which a dive is either safe or unsafe according to the value of the tissue ratio compared with the critical ratio. Early deterministic models based on Haldane’s theory of supersaturation (see Haldane Theory) sought to minimize DCS incidence by using lower tissue ratios (Tikuisis and Gerth, 2003). The models assumed no bubble formulation and that the dive would be ‘safe’ if the critical supersaturation ratio was not exceeded during ascent. Many established decompression limits were derived empirically, and the use of the early deterministic models to project ‘safe’ decompression limits to longer deeper dives resulted in unacceptably high incidents of DCS (Tikuisis and Gerth, 2003). The original version of the LE model was deterministic and similar to many Haldane models except that inert gas exchange kinetics was linear when excess supersaturation was present.

1.5 Inert Gas Differences

Divers breathe a mixture of oxygen and inert gas because oxygen alone is toxic and can cause convulsions if breathed at too great a pressure. Currently, divers use two main inert gases, helium and nitrogen, in their breathing mixtures. Most recreational divers use compressed air, 21% oxygen and 79% nitrogen, which is low cost and readily available. The main disadvantage of nitrogen is that it is narcotic at increasing depths and generally is not used deeper than 150-200 feet seawater (fsw). (A rule of thumb, called Martini's law, states that with every 50 feet of depth, the narcotic effect of nitrogen is equivalent to drinking one martini.) Enriched air nitrogen mixtures, also called nitrox, raise the percentage of oxygen in the mixture and have the advantage of reducing the decompression obligation because less nitrogen is absorbed. To limit the risk of oxygen toxicity due to the additional oxygen, nitrox is generally not used deeper than 130 fsw (Hamilton and Thalmann, 2003).

Helium is not narcotic at depth, which makes it advantageous for deep diving. A helium-oxygen mixture is referred to as heliox. Trimix, a third type of mixture, is a combination of helium, nitrogen, and oxygen but will not be discussed in this paper.

Behnke and Willmon discovered that helium was absorbed or eliminated from the body at about twice the rate of nitrogen (Behnke and Willmon, 1941). The reasons for this are the differences in solubility of helium and nitrogen in blood ($\_{b}$) and tissue ($\_{t}$).

Table 2 shows values for the solubility of nitrogen and helium measured in blood and olive oil. An aqueous tissue such as muscle has an inert gas solubility similar to that of blood while the inert gas solubility in fat is often assumed to be similar to that of olive oil.

	Nitrogen	Helium
_blood	0.0112 ml ml^{-1} ATS^{-1}	0.0085 ml ml^{-1} ATS^{-1}
_fat	0.052 ml ml^{-1} ATS^{-1}	0.0168 ml ml^{-1} ATS^{-1}

Table 1: Solubility of helium and nitrogen in different tissues (Weathersby and Homer, 1980).

Recalling equations (3) and (4), the halftime can then be expressed as

(5)

If the perfusion (Q_{vt}) is assumed to be 2 ml/min/100 ml tissue (a typical rate for resting muscle), the halftimes of nitrogen and helium in an aqueous tissue are the same and equal to 34.65 minutes. For a fatty tissue, however, the nitrogen halftime is 160.88 minutes while the helium halftime is 68.48 minutes. The fat content of the body was the basis for how Behnke and Wilimon (1941) explained the more rapid exchange of helium over nitrogen. However, at saturation, the concentration of nitrogen in fat is 3.1 times higher than that of helium as indicated by the ratio of helium to nitrogen solubility in fat (Tikuisis and Gerth, 2003).

1.6 DCS Probability and Epidemiology

Deterministic models assign a value of ‘safe’ or ‘unsafe’ to a dive depending on whether the ascent did not exceed the critical ratio of supersaturation. In practice, however, one diver might develop DCS while others will ascend safely following the same depth-time profile. Therefore, a given dive profile cannot be described as either 'safe' or 'unsafe.' A more appropriate measure of safety is the probability of DCS associated with the dive. It is up to the individual diver (or organization) to decide what probability is safe. Only a probabilistic approach to decompression can explicitly model the DCS outcome (Tikuisis and Gerth, 2003).

The probabilistic approach associates a DCS probability with each dive and fits a probability function to a set of binary data, the occurrence or non-occurrence of DCS. In a probablistic extension of a deterministic model, the tissue ratio might be considered as an instantaneous measure of decompression stress that is transformed into a probability variable having a value between zero and one. This transformation is accomplished using functions such as the Hill or logistic equations (Weathersby et al., 1984). Logistic regression is a well developed method for estimating probability (Hosmer and Lemeshow, 1989) and is used in this thesis to illustrate the process for assessing the association of decompression outcomes with potential explanatory variables. More complex approaches to the estimation of probability have been used, such as the survival models employed by the U.S. Navy, but these are beyond the scope of this thesis (Tikuisis and Gerth, 2003).

Decompression models require extensive testing to support claims of safety. For example, 72 trials of a given dive profile must be conducted with no incidence of DCS to declare an upper limit of 5% DCS with a 95% binomial confidence using a deterministic model. If one incident of DCS occurs, then 109 trials are required, to make the same 5% risk declaration (Tikuisis and Gerth, 2003). The advantage of probabilistic modeling is that it allows the combination of data from many dive profiles. The larger number of tests narrows the width of the confidence interval improving the reliability of the results.

Epidemiologists use a construct called the epidemiological triad to explain how different factors, external and internal, affect a person's susceptibility to a disease (Friedman, 1974). The epidemiological triad attributes a disease outcome to the presence of the cause of the disease (the agent), internal personal factors (the host), and external factors (the environment). The exposure (depth-time profile and inspired gases) is the cause of DCS, but a diver's susceptibility to DCS might also be influenced by his physical characteristics and environmental factors. The diver's personal characteristics might include age, weight, height, existing medical conditions, etc. Environmental factors might include immersion, exercise, water temperature, etc.

1.7 Probabilistic LE1 and Multi-gas Models

In deterministic models based on Haldane theory, the decompression is controlled at any one time by only one of the many different tissue compartments; this assumes that DCS can only occur in that one compartment. Probabilistic models assume that DCS is able to occur in any of the modeled compartments and that DCS occurrence in that compartment is independent of any of the other compartments (Tikuisis and Gerth, 2003). The deterministic LE gas exchange model developed by Thalmann was reconfigured into a probabilistic version for N_2O_2 breathing mixes and called the USN Linear-Exponential (LE1) probabilistic DCS model (Parker et al., 1992; Thalmann et al., 1997).

The LE1 model was used to estimate the conditional probability of DCS based upon a mathematical simulation of in vivo bubble growth (Thalmann et al., 1997). The conditional probability of DCS (cPDCS) is defined as the probability of DCS during or after a dive, based on the condition that the diver is DCS free upon reaching the surface. The cPDCS increases linearly from zero at the start of the dive and reaches a maximum value at the start of the next dive (if within 24 hours) or at a time within 12 hours of surfacing from the day's last dive (Dunford, 2003). The single gas LE1 probabilistic model was later revised to account for multiple inert gases and named the multi-gas linear exponential model, or LEM (Parker et al., 1998).

1.8 Doppler Bubble Detection

Doppler ultrasound is a non-invasive method for measuring the presence of bubbles in circulating blood, known as venous gas emboli (VGE). Because gas bubbles scatter ultrasonic signals more efficiently than do red blood cells, they produce an increased signal which, when electronically converted to an audible signal, is easily distinguished from the background blood flow or heart sounds. The signal contains both amplitude and frequency information and, with training, is a simple method for scoring bubble activity (Nishi et al., 2003).

The most common sites to detect venous gas emboli (VGE) by Doppler monitoring are: the precordium (right ventricle/pulmonary artery), right subclavian vein, and left subclavian vein (shoulder). Each site is monitored with the subject at rest and then after movement, either a hand squeeze for the subclavian site or a leg movement for the precordium. Movement often precipitates a shower of bubbles which makes detection easier (Nishi et al., 2003).

The Kisman-Masurel (KM) and Spencer classification systems are the principal methods by which VGE are scored. The KM method separates the bubble signal into three components, each measured on a 0-4 scale. These components describe bubble frequency per cardiac period, percentage of cardiac periods with bubbles, and amplitude of bubble sounds compared to cardiac sounds. The resulting triplet is called the KM score.

The Spencer scoring system classifies VGE as grades 0 to IV, based on number of bubble signals per cardiac cycle and number of cardiac cycles containing bubbles (Nishi et al., 2003). There are provisions to translate scores from KM to Spencer as shown in Table 3. The + or – will be omitted in our application of the conversion of KM to Spencer scores.

Grade	Spencer code	KM code (bubble grade)
0	A complete lack of bubble signals	
I	An occasional bubble signal discernible with the cardiac motion signal with the great majority of cardiac periods free of bubbles	111(I-), 112(I), 113(I), 211(I-), 212(I), 213(I+)
II	Many, but less than half, of the cardiac periods contain bubble signals, singly or in groups	121(I+), 122(II), 123(II), 212(II-), 222(II), 223(II+)
III	Most of the cardiac periods contain showers of single-bubble signals, but not dominating or over-riding the cardiac motion signals.	232(III-), 233(III), 242(III), 243(III), 332(III), 342(III+), 343(III+)
IV	The maximum detectable bubble signal sounding continuously throughout systole and diastole of ever cardiac period and over-riding the amplitude of normal cardiac signals.	444(IV)

Table 1: Description of scales for grading bubbles (Nishi et al., 2003).

The occurrence of venous gas emboli is abnormal, although it is not necessarily pathological for DCS. There is not a one-to-one correlation of VGE to DCS that would indicate absolute causality, however the detection of bubbles in the venous blood is thought indicative of bubbles elsewhere in the body. In addition, the KM or Spencer scores have been found to be statistically associated with DCS incidence (Gault et al., 1995). Divers exhibiting Spencer bubble grades of III and IV were found to have a greater incidence of DCS than those with bubble grades of 0, I, or II. Because of the statistical association of Doppler score with DCS, the Canadian Forces have used Doppler signals as a less dangerous end-point than DCS for developing decompression procedures (Nishi, 1987; 1989; 1991; 1992). In this thesis, bubble grades III or IV will be called high bubble grade (HBG). A variable HBG will be defined as HBG=0 for bubble grades 0, I, II and HBG=1 for bubble grades III or IV.

1.9 Mechanisms and Severity of DCS

The signs and symptoms of DCS vary in severity and are typically divided into two categories, Type I and Type II. One of the most common DCS symptoms, joint or muscle pain, is defined as Type I DCS. Type II DCS signs and symptoms involve the central nervous system, either the spinal cord or brain. Weakness, paralysis, or sensory changes (numbness or tingling) indicate spinal DCS. Cerebral DCS symptoms include disorders of consciousness such as slurring of speech, memory loss, and loss of coherence. Neurological DCS (Type II) is more serious than Type I DCS because the symptoms are more severe and have the potential for permanent damage.

The pathophysiology of neurological DCS appears to be different than that of Type I DCS. The limb pain of Type I DCS is believed to be caused by stationary extravascular bubbles in tissue, particularly around joints (Vann, 2003 chapter 7). Cerebral symptoms, on the other hand, are widely believed to be caused by venous bubbles that pass into the arterial circulation (Francis, 2003). The lungs serve as a filter for VGE originating in the tissues, but VGE can escape the pulmonary filter by several mechanisms and enter the arterial circulation. One such mechanism is a small hole in the wall of the heart between the right and left atria called a patent foramen ovale (PFO) that can allow bubbles to bypass the lung filter and enter the systemic arterial circulation.

Another mechanism, called transpulmonary passage, occurs when VGE are very numerous and overwhelm the lung filter or when the bubbles are small enough to pass through the pulmonary capillaries (Vann, 2003 chapter 7). It is less certain if arterial bubbles play a role in spinal DCS, but this has been proposed as one potential mechanism (Francis, 2003).

1.10 VGE and DCS Data

Data on which to base an investigation of the associations of DCS and VGE is not abundant or readily available. A small study conducted at Duke reported the results of manned decompression trials of the Mk15 underwater breathing apparatus (UBA) (Vann, 1982). The Mk15 is a closed circuit UBA that uses the diver's lungpower to move the breathing gas through a carbon dioxide scrubber and into a counter-lung, maintaining a constant volume in the system. The Mk15 controls the partial pressure of oxygen to a constant value (usually 0.7 atmospheres) called a set point, using oxygen sensors in the circuit and an automatic oxygen addition system (Nuckols et al., 1996). The oxygen is diluted by a diluent gas, usually nitrogen or helium, to avoid oxygen toxicity.

The primary objective of the Duke study was to develop a decompression calculation method that could be used to study the effects that exercise, oxygen partial pressure, and inert gas have on decompression. Secondary objectives were to investigate the relationships between decompression sickness, gas bubbles in the blood, and changes to the blood (Vann, 1982). The Duke study did not try to develop operational decompression schedules.

The Duke study tested different conditions of exercise, immersion, oxygen partial pressure, and inert gas. No-decompression dives were conducted for each gas to 60, 80, 100, 120, and 150 fsw. In addition, twenty-nine decompression profiles were tested, 26 with nitrogen and 3 with helium mixes.

The Duke study found that the inert gas in the breathing mix was statistically associated with Type II DCS and with more incidents of high bubble grade (Spencer score >2) after helium dives (Table 4). Figure 2 shows the increased incidence of HBG with helium breathing mixes compared to nitrogen breathing mixes. The error bars represent the 95% binomial confidence limits. The relation of inert gas to all DCS outcomes is illustrated in Figure 3. Type I DCS and all DCS together were not associated with inert gas.

	Total	Nitrogen	Helium	p-value
# Dives	552	435	117	
# DCS	24	19	5	
DCS Incidence	0.043	0.044	0.043	0.965
# DCS I	18	17	1	
DCS I Incidence	0.033	0.039	0.009	0.099
# DCS II	6	2	4	
DCS II Incidence	0.011	0.005	0.034	0.006
# HBG	67	43	24	
HBG incidence	0.134	0.112	0.205	0.01

Table 2: Significant results of Duke Study, relation of inert gas to HBG and DCS II.

Figure 0: HBG incidence in Duke study listed by inert gas. The number of HBG events and dives appears as a ratio over the 95% binomial confidence limits.

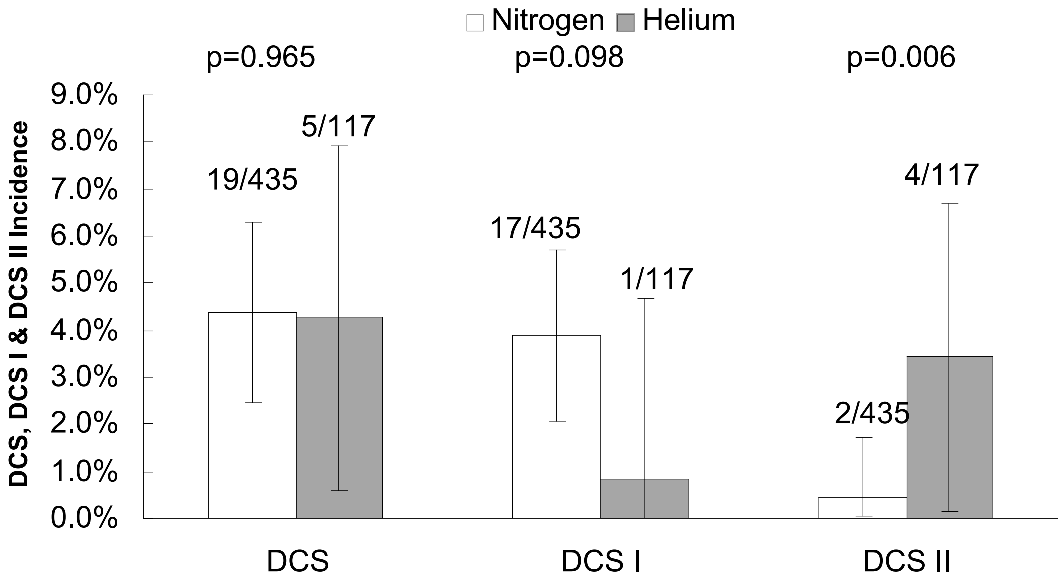

Figure 0: DCS incidence in Duke study listed by inert gas. The number of DCS events and dives appears as a ratio over the 95% binomial confidence limits.

All DCS outcomes were found to be statistically associated with HBG. These relations are illustrated in Figure 4. The diver characteristics of age and weight were found to be significantly associated with HBG but not with DCS, illustrated in Figures 5 and 6.

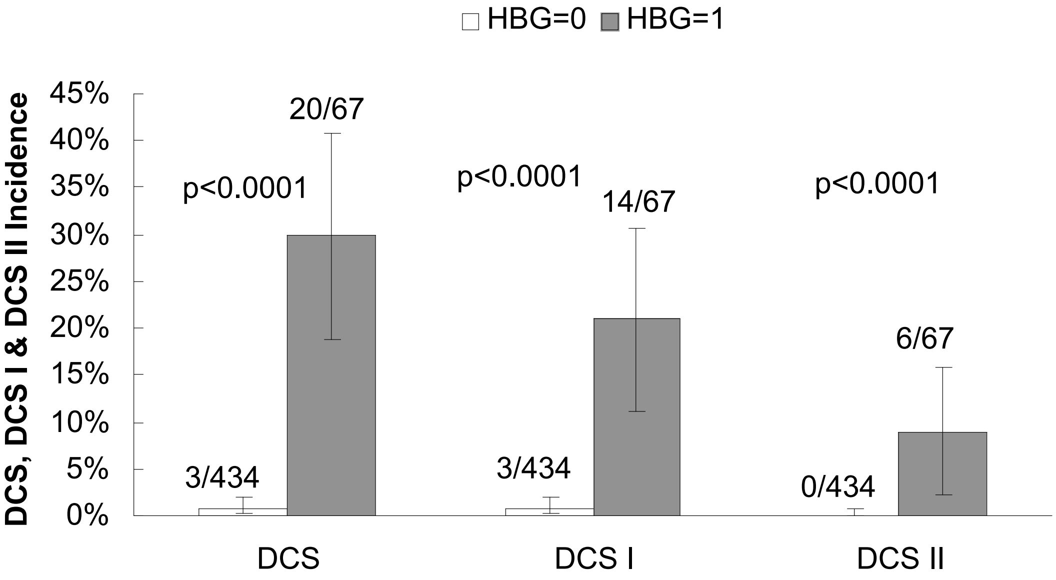

Figure 0: DCS incidence in Duke study listed by HBG. The number of DCS events and dives appears as a ratio over the 95% binomial confidence limits.

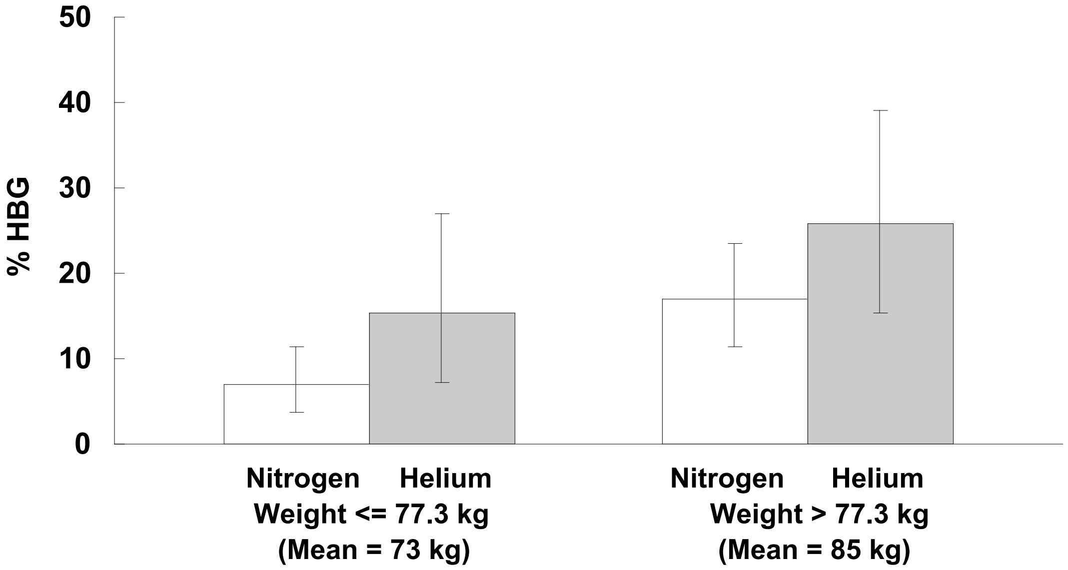

Figure 0: Effect of weight (above and below the median of 77.3 kg) on HBG incidence in the Duke study.

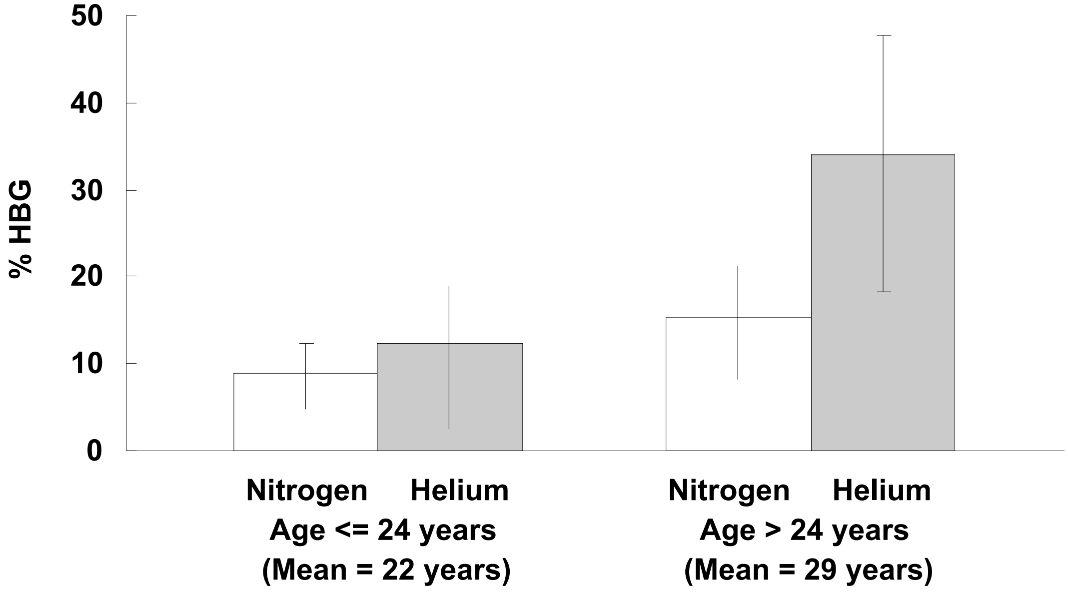

Figure 0: Effect of age (above and below the median of 24 years) on HBG incidence in the Duke study.

The U. S. Navy conducted a larger set of decompression trials using the Mk 15 and 16 rebreathers in the early 1980's. The purpose of these trials was to develop a deterministic decompression model for Navy divers (Thalmann 1985, 1986). There were numerous different helium and nitrogen profiles tested during these studies with a total of 2419 man dives. Doppler monitoring was performed on each diver after every dive, but the Doppler data were not analyzed.

1.11 Objectives

This thesis will attempt to confirm the observations of the Duke data through analysis of the larger dataset from the U.S. Navy Mk 15/16 decompression trials. The Duke observations were: a) VGE were more common with helium gas mixes than with nitrogen mixes; b) helium had a higher incidence of Type II DCS than did nitrogen; and c) diver characteristics of age and weight were significantly associated with HBG outcomes.

2 Methods

2.1 Data Management

All data discussed below were from studies involving human subjects that were approved by Institutional Review Boards (IRB) at the Duke Medical Center and the Navy Experimental Diving Unit (NEDU). The Duke IRB also approved a retrospective analysis of these data. The sources for the Navy data included the NEDU reports (Thalmann, 1985; 1986) and raw Doppler data from research notebooks and logbooks provided by Dr. Thalmann who was the principal investigator for both NEDU studies.[1]

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[1] Thalmann, Personal communication

The NEDU dives were conducted immersed in a wet pressure chamber. The divers performed intermittent light exercise while at depth on electrically-braked bicycle ergometers and rested during ascent or decompression stops. Table 5 and Table 6 provide a summary of the NEDU dives. On no-decompression (no stop) dives the diver ascended directly to the surface at 60 feet per minute. A repetitive dive means the diver made another dive on the same day after a designated surface interval. A square dive describes a profile where the diver stayed at one depth at the bottom and surfaced according to the required decompression. A multi-level dive is a dive where the diver spent time at two or more depths while on the bottom and then surfaced according to the decompression requirements.

Report	Gas	# Divers	# Profiles	# Man Dives	# DCS incidents
Thalmann, 1985	Helium	174	47	1582	59 total 22 Type II
Thalmann, 1986	Nitrogen	126	38	837	50 total 8 Type II

Table 3: General statistics from Navy Mk 15 Decompression Trials by report.

	Air Square Dive (50-190 fsw)	0.7 ATA PO_2 in N_2 (100 and 150 fsw)	Air on Bottom 0.7 PO_2 during Deco (60, 100, and 150 fsw)	Air Repetitive (80, 100, 120, and 150 fsw)	Long duration multilevel Dive with switches from air to 0.7 ATA PO_2 (20-100 fsw)
Decompression	14	4	3	3	2
No-stop	5			7	

The profiles in 1-85 were all square dives using a constant 0.7 ATA oxygen partial pressure in helium with 18 of 47 profiles being no decompression dives. The profile depths tested in the 1-85 square dives were: 60, 80, 100, 120, 140, 150, 160, 180, 200, 250, 260, and 300 fsw. Seventy-nine man dives on helium involved switching from helium to nitrogen during decompression which made the effects of inert gas on outcome ambiguous. These dives were not included in the analysis.

The Doppler records from the Navy data were contained in notebooks with 600 pages. Each page was marked with a date and tape recording number and contained diver names and the Doppler scores at successive monitoring times. These scores corresponded to a particular dive in the series and each dive was designated by an alphanumeric code.

Most of the Navy Doppler data were recorded using the KM scoring method. (386 dives were recorded using the Spencer system.) The Doppler scores were recorded with one series of scores taken at rest (precordial, left subclavian, and right subclavian) and three series taken after movement. The KM scores from the data were transformed to the Spencer bubble scores using Table 3. After transformation, only the maximum VGE score for all sites and measurements was retained to describe the VGE outcome of each dive and diver. This assumed that the maximum VGE score was a measure of decompression stress for that dive and diver. The 5-point Spencer scale was then converted to a binary system, high bubble grade (HBG), where HBG=0 for Spencer grades 0, I, and II and HBG=1 for Spencer grades III and IV.

A Microsoft Access database was created to link the Doppler readings for individual divers to the corresponding dives. Each dive was matched with its corresponding dive profile using the date of dive.[2] Each diver's age, weight, and height were listed using a numeric identifier in NEDU Reports 1-85 and 8-85 (Thalmann, 1985; 1986). The numeric identifier was also listed with each profile and date of dive, but the

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[2] Personal communication, Thalmann

key to this code was unavailable. To link the Doppler records, diver names, dive profiles, diver physical characteristics, and DCS outcomes, Dr. Thalmann's personal logbooks were used to determine who was on each dive. Each logbook entry contained the names of the divers, the date the dive occurred, and the alphanumeric code for the dive. Using a process of elimination, the code key was broken to establish links between Doppler scores and dive information. The divers were then reassigned new numerical identifiers and all information was entered into the Access database.

2.2 Empirical Variables

The dependent, or outcome, variables of the study were the occurrences of DCS and HBG. DCS was subdivided into Type I decompression sickness (DCS I) and Type II decompression sickness (DCS II). The independent or potential explanatory variables that represented the exposure were experimentally controlled. These variables included: dive depth (D1), time (T1), total time in decompression schedule (TDT), inert gas, oxygen partial pressure or oxygen fraction, and a derived term, PrT, suggested by Hempleman (Hempleman, 1993). PrT represents a measure of the inert gas absorbed in a cartilage-like tissue while at depth during a square dive and is obtained by multiplying dive depth by the square root of dive bottom time. The PrT concept is not accurate for repetitive or multi-level dives and only will be applied to the last dive in a repetitive series as an approximate measure of decompression stress.

The diver characteristics were not experimentally controlled but were recorded. These included age, height, weight, and percent body fat. Percent body fat was not recorded for all divers, so it was not included with the other variables during analysis. The effect of body fat was evaluated separately. Diver height and weight were transformed into a new variable, Body Mass Index (BMI), by dividing weight (in kg) by height (in meters) squared. These uncontrolled variables were tested as potential confounders to the experimentally controlled exposure variables in the models.

The construct of the epidemiological triad motivated the classification of the observed variables and formulation of the models used to predict the outcome variables. The experimentally controlled variables that describe the exposure correspond to the agent. The uncontrolled diver characteristics that serve as potential confounders correspond to the host factors. The environmental conditions, immersion, exercise, and temperature, were experimentally controlled and the same for both the helium and nitrogen series of trials. Hence, the environmental factors are not considered in this analysis.

In this study, dives and divers were assumed to be independent. This means that the outcome of each trial was independent of all the others and the probability of an outcome was completely described by the observed variables.

2.3 Statistical Analysis

Descriptive and regression analysis were conducted using SAS software (Version 8.1, Cary, NC). The mean values of age, height, weight, BMI, and percent body fat were computed to identify possible differences in the diver population with regard to inert gas, HBG, and DCS. The raw incidences of HBG, DCS, DCS I and DCS II were determined using two-by-two statistical tables in SAS. The association of inert gas to all outcomes, the association of diver characteristics to all outcomes, and the association of HBG to DCS outcomes were tested using the Cochran-Mantel-Haenszel procedure in SAS.

The possibility that apparent differences in raw outcome of HBG, DCS, DCS I, and DCS II are due to differences in exposure severity or diver characteristics must be evaluated to reduce the chance of incorrect conclusions. For example, an increased incidence of HBG or DCS in helium dives might be because the helium trials contained inherently “riskier” profiles or the divers breathing helium were older and fatter than those during the nitrogen trials. To decrease the possibility of such error, the association among the outcomes with the principal variables of interest (inert gas and HBG) were investigated using logistic regression with statistical controls for exposure severity and diver characteristics.

Logistic regression allows the estimation of binary outcomes using a mixture of continuous and dichotomous variables. The outcome variables, HBG, DCS, DCS I, and DCS II, are dichotomous with a value of one for DCS (or HBG) and a value of zero for no DCS (or no HBG). The corresponding probabilities of DCS and no DCS are P and (1-P) where P has a value between zero and one. The predictor variables in logistic regression can be of any form and do not have to have a specific distribution. The form of the logistic equation is

$$\text{logit} = \ln[P/(1-P)] = \_{}_{0} + \_{}_{1}x_{1} + \_{}_{2}x_{2} + \ldots + \_{}_{i}x_{i} \qquad (6)$$

where the _’s are unknown constants to be estimated and the x’s are continuous, ordinal, binary, or indicator predictor variables. Logistic regression is useful for evaluating predictor variables because it is linear in the logit. Predictor variables can be tested one by one to determine which are significantly associated with the outcome variables, and significant variables can then be tested as a group. A step by step approach was adopted beginning with simple models and building to the more complex.

In regression analysis, the measure of fit of a mathematical model to data is described by a loss function, for example, the mean squared error in linear or curvilinear regression. The logistic equation models the probability of dichotomous variables using a loss function called the likelihood, where the likelihood of a trial equals the probability of every observed outcome in the trial multiplied together. In the context of this thesis, an event represents the occurrence of DCS (DCS=1) or HBG (HBG=1) and a non-event represents DCS=0 or HBG=0.

(7)

The likelihood is a very small number, so the natural log of the likelihood, or log likelihood, is generally reported. The log likelihood (LL) is a negative number.

The method of maximum likelihood applies a DCS model to the data and adjusts the model parameters (_’s) until the theoretical predictions of the model and the experimental data are in the closest possible agreement. This occurs when the maximum likelihood is achieved (Weathersby et al., 1984). SAS performs this optimization automatically for models having the form of equation (6). For the negative LL, the maximum LL is achieved when its absolute value is smallest.

2.3.1 Methods of Model Evaluation

It is useful to have upper and lower bounds on maximum likelihood to which various models may be compared. These limits are provided by the log likelihoods for the null and the exact models. The null model is the raw incidence of the outcome for the entire study and assumes that none of the predictor variables are important. In the null model of logistic regression (equation 6), all the _'s are set equal to 0 except for _$_{0.}$ No model should have a more negative maximum log likelihood than the null model. The log likelihood for the null model is computed from equation (7) where observations is the number of individual exposures for the entire trial and events is the number of divers for whom DCS or HBG is one.

The exact model describes the observed data perfectly and serves as an upper limit because no continuous model can have a less negative log likelihood (Weathersby et al., 1984). The log likelihood of the exact model computes the log likelihood for each individual dive profile as for the null model and sums these values to compute the log likelihood for the exact model. The number of degrees of freedom for the exact model is equal to the total number of dive profiles.

The c-index is another measure to judge the goodness of fit of the model predictions and is listed with the maximum likelihood for each model. The c-index can be used as a means to "normalize" the likelihoods of the null and exact model for comparison with the nested models. A c-index of 1 indicates a perfect fit to the data, which corresponds to the exact model. A completely random fit, with no predictive power, is indicated by a c-index of 0.5. It is analogous to flipping a coin that is "weighted" to describe the observed outcome of the study. The null model has a c-index of 0.5.

Models in the form of equation (6) are described as nested models. The general or complete model contains all the possible variables, x's, with non-zero _'s. In the nested models, some of the _'s in the complete model are set to zero, which allows different nested models to be statistically compared. The degrees of freedom in a nested model are the number of _'s whose values are estimated by maximum likelihood.

The method used to compare differences in statistical significance among nested, null, and exact models is called the likelihood ratio test. To see if there is an improvement when one model is selected over another, the likelihood ratio test compares the ratio of the likelihoods of two hypotheses. When using the log likelihood, the likelihood ratio test can be expressed as the difference of the log likelihoods because differences of logarithms are the same as ratios (Weathersby et al., 1984):

(8)

The significance of an improvement in LL can be determined because the likelihood ratio is distributed as a _^{2} variable (Weathersby et al., 1984). The difference in the degrees of freedom between two models determines the degrees of freedom of the likelihood ratio. If the difference in two likelihoods is not greater than the tabulated value of _^{2} at the 0.05 confidence level for the number of degrees of freedom, then there is no significant improvement. The values used to determine significant improvement in the models, based on the difference in the value of -2LL, are contained in Table 7.

Degrees of freedom	1	2	3	4	5	6	7
_^{2} value (-2LL difference)	3.841	5.991	7.815	9.488	11.07	12.592	14.067

Table 3: Values used in LR test to measure significance of model improvement.

2.3.2 Tests of Outcome Associations with Predictor Variables

The analysis began by investigating the raw data for statistical association of the outcome variables (HBG, DCS, DCS I, and DCS II) with inert gas and HBG using the Cochran-Mantel-Haenszel (CMH) test and logistic regression. While both procedures can assess association, logistic regression also provides a measure of the strength of the association through the c-index and odds ratio (see below). Thus, a simple significance test can be viewed as a one-parameter model.

Following tests of the raw data, HBG was modeled using inert gas and three measures of diving exposure (empirical, Haldane tissue tension, cPDCS). DCS outcomes were first modeled using inert gas and exposure and then by HBG as an additional predictor variable. The diver's physical characteristics were introduced next as possible confounders and the "complete" model was run for all outcomes using the selection methods in SAS that found the best fit of the model to the data as determined by maximum likelihood and the likelihood ratio test. The selection methods eliminated non-significant predictor variables thus obtaining the most parsimonious model. This was done for all outcome variables.

Once the significant predictor variables have been determined, the importance of their contribution to the model can be evaluated using the odds ratio. The odds ratio is a measure of association that approximates how much more likely, or unlikely, it is for an outcome to be present given the value of the independent predictor variable (Hosmer and Lemeshow, 1989). For dichotomous predictor variables, where x=1 or x=0, the odds ratio (OR) is the ratio of the outcome probability for x=1 to the outcome probability for x=0, or:

$$OR = \frac{P(1)/[1 - P(1)]}{P(0)/[1 - P(0)]} \qquad (9)$$

If OR=2, for example, the outcome occurs twice as often when the dichotomous predictor is present than when it absent. The log odds ratio, obtained by taking the log of equation

(9), is defined as the difference in the logit (equation 6). When continuous variables are used in logistic regression it is assumed that the logit (equation 6) is linear in the variable of interest (Hosmer and Lemeshow, 1989), which can be expressed:

$$g(x) = \beta_0 + \beta_1 x_1 \qquad (10)$$

The slope coefficient _$_1$ corresponds to the change in the log odds for an increase of one unit of x_1. However, changes in one unit of a variable (e.g., one minute) are not always of interest to the researcher. The log odds can be obtained for an arbitrary change of c units in x_1 (e.g., 10 min) from the logit difference expression:

$$g(x + c) - g(x) = c\beta_1 \qquad (11)$$

The associated odds ratio is obtained by exponentiating the result of equation (11) (Hosmer and Lemeshow, 1989). If the odds ratio is greater than one, the probability of the outcome increases by that many times as the predictor increases by one unit. If the OR is less than one, the probability of the outcome decreases as the predictor increases.

2.3.3 “Physiological” Haldane Tissue Model

While empirical tests can determine which outcome and predictor variables are statistically associated, these predictors are of limited value for determining the probability of an outcome for a particular exposure. Predicting this probability is the ultimate goal, like predicting whether a particular exposure was safe or not safe was in the Haldane decompression algorithm. The potential of a simple physiological model based on a single, well mixed Haldane tissue to make such predictions was assessed.

In the single tissue model, an estimated inert gas tissue tension was computed at the end of each dive using equation (2) after stepping through all stages of the dive. This tissue tension transformed the entire exposure (depth-time profile, oxygen, inert gas, and exercise) into a single variable that became a predictor variable in equation (6). Recalling equations (3) and (4), a change in perfusion or inert gas solubility determined the rate of inert gas exchange as defined by the time constant, *k*, or tissue halftime, $T_{1/2}$. In the well-stirred tissue model, the effects of exercise, immersion, and inert gas on HBG and DCS are reflected in changes in the inert gas exchange rate as determined by the time constant, *k*.

The effect of exercise at depth cannot be tested directly as an empirical variable in logistic regression as it was the same in all exposures, but it can be incorporated as a parameter in the tissue model defined by equation (2). Exercise can be expressed as a multiplier of the gas exchange constant *k*, where the baseline state is a diver at rest breathing nitrogen-oxygen, or $k = k_{N2}$. If exercise is present at depth, as in all the Navy dives, the appropriate *k* will be multiplied by a constant, c_{ex}, to account for the effect of an increase in blood flow.

If the diver is breathing helium, *k* will be determined by multiplying k_{N2} by the ratio of the nitrogen to helium partition coefficients, *chn*. The *chn* factor may be derived by solving equation (3), the expression for *k*, for perfusion, Q. Perfusion can be expressed as the ratio of the time constant to the partition coefficient for both nitrogen and helium giving:

$$Q = \frac{k_{N2}}{\left(\frac{\alpha_b}{\alpha_t}\right)_{N2}} = \frac{k_{He}}{\left(\frac{\alpha_b}{\alpha_t}\right)_{He}}$$

Solving this expression for k_{He} gives,

$$k_{He} = chn \cdot k_{N2}$$

where *chn* is the ratio of the partition coefficients for helium and nitrogen, or

Thus, the time constant for any combination of inert gas or exercise is

$$k = k_N * chn * c_{ex}$$

where $chn = c_{ex} = 1$ if nitrogen-oxygen is the breathing gas at rest.

The parameters k_{N2}, c_{ex}, and *chn* were used in the calculation of the inert gas tissue tension (equation 2) which became an explicit predictor in logistic regression (equation 6). As these parameters do not appear in equation (6), their optimal values cannot be automatically determined by SAS. The optimization was accomplished by an iterative grid search. First, *chn* and c_{ex} were fixed to values of one, and the value of k_{N2} was varied until its optimal value was found according to maximum likelihood. Second, k_{N2} was fixed to this value, c_{ex} was fixed at one, and the optimal value of *chn* was found. Third, k_{N2} and *chn* were held constant while the optimum value of c_{ex} was determined. The optimal value of k_{N2} was again determined with the adjusted values of *chn* and c_{ex}. These steps were repeated until there were no further changes to k_{N2}, *chn*, and c_{ex}. The process was repeated when the uncontrolled diver characteristics were added.

Inert gas was an inherent property of the tissue model but was also an experimentally controlled variable. To determine if inert gas was adequately described by the Haldane tissue, an explicit inert gas variable was added to the logistic regression (equation 2) as a predictor. If there was no significant improvement in the maximum likelihood, this would indicate the tissue model accounted for inert gas adequately. If, on the other hand, inert gas significantly improved the model fit, this would indicate that the model was an incomplete representation of inert gas.

The "physiological" Haldane tissue models are not like the above nested empirical models. The difference arises because the optimal values for the parameters that determine the tissue tension are not accounted for within the _ for the Pt variable. The likelihood ratio test can, therefore, not be used to compare the empirical and "physiological" models. The c-index will be used to show the relative difference between the two sets of models.

2.3.4 Conditional Probability of DCS as an Exposure Variable

All dive profiles in the Navy data were run using the LEM to determine conditional probability of DCS[3], which was then used as a measure of exposure severity. The explicit control for exposure severity is important because it allows the determination of whether increased bubble scores were due to the inert gas itself or the presence of riskier dives. The nitrogen-oxygen form of this program was successfully used in a previous study to determine exposure severity in an analysis of VGE in recreational divers (Dunford et al., 2003). The helium-oxygen form of this program was used on profiles from NEDU 1-85 (Thalmann, 1985) and the nitrogen-oxygen form was used on the profiles from NEDU 8-85 (Thalmann, 1986). Because there were profiles which had missing cPDCS values (166 dives), those profiles were eliminated. The analysis of the empirical and conditional probability models was performed using this reduced data set in order to ensure accurate comparison.

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[3] Personal communication, Dr. Wayne Gerth, NEDU

The procedure used in evaluating the empirical models was repeated, replacing the exposure variables by the derived conditional probability of DCS (cPDCS) from the LEM. The models were started using only cPDCS and then inert gas was added to determine if the formulation for cPDCS completely accounted for inert gas. HBG was added as another predictor variable for the DCS models. Diver characteristics were added to complete the general model, and then the general model was run using SAS selection procedures to get the best model and determine the significant predictor variables.

3 Results

3.1 General Statistics

After deletion of 79 dives that used both helium and nitrogen, the Navy dataset used contained 2381 Doppler records including 873 nitrogen dives and 1508 helium dives. Of the 2381 dives, there were 861 incidents of HBG, 74 incidents of DCS I, and 28 incidents of DCS II. The raw incidence of the outcome variables was determined using two by two statistical tables in SAS. The results showed that the incidence of HBG and all types of DCS were related to inert gas. Table 8 shows incidence of HBG related to inert gas, also illustrated graphically in Figure 7. When comparisons between the conditional probability and empirical models were performed, an additional 166 dives were eliminated because cPDCS values were not available for those profiles.

	Total	Nitrogen	Helium	p-value
# Dives	2381	873	1508	
# HBG	861	215	646	
HBG Incidence	0.362	0.246	0.428	<.0001

Table 3: Relation of inert gas to HBG outcome in Navy data.

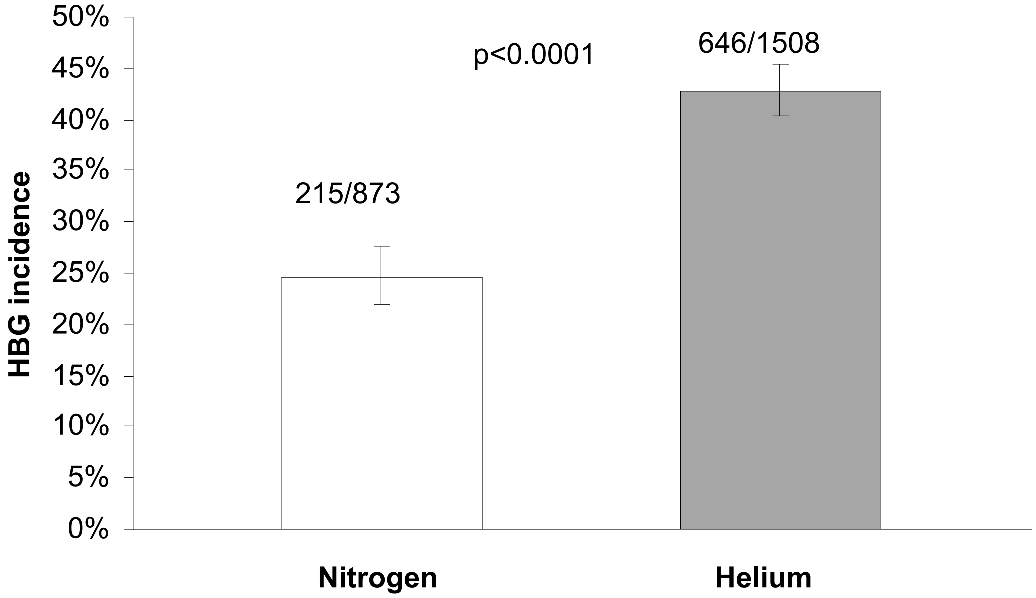

Figure 0: HBG incidence in Navy data by inert gas. The number of HBG events and dives appears as a ratio over the 95% binomial confidence limits.

Table 9 shows the relation of DCS outcomes to inert gas and is also illustrated graphically in Figure 8. More incidents of DCS II occurred with helium than with nitrogen, although the difference was not statistically significant. Nitrogen dives had increased incidence of all DCS and Type I DCS and these relations were found to be statistically significant.

	Total	Nitrogen	Helium	p-value
# Dives	2381	873	1508	
# DCS	102	47	55	
DCS Incidence	0.043	0.054	0.036	0.046
# DCS I	74	40	34	
DCS I Incidence	0.031	0.046	0.023	0.002
# DCS II	28	7	21	
DCS II Incidence	0.012	0.008	0.014	0.198

Table 3: Relation of inert gas to DCS incidence in Navy data.

Figure 0: DCS incidence in Navy data listed by inert gas. The number of DCS events and dives appears as a ratio over the 95% binomial confidence limits.

The raw incidences of all DCS outcomes were significantly associated with HBG. These results are illustrated in Table 10 and Figure 9.

	Total	HBG=0	HBG=1	p-value
# Dives	2381	1520	861	
# DCS	102	40	62	
DCS Incidence	0.043	0.026	0.072	<.0001
# DCS I	74	29	45	
DCS I Incidence	0.031	0.019	0.052	<.0001
# DCS II	28	11	17	
DCS II Incidence	0.012	0.007	0.02	0.007

Table 3: Relation of HBG to all DCS outcomes in Navy data.

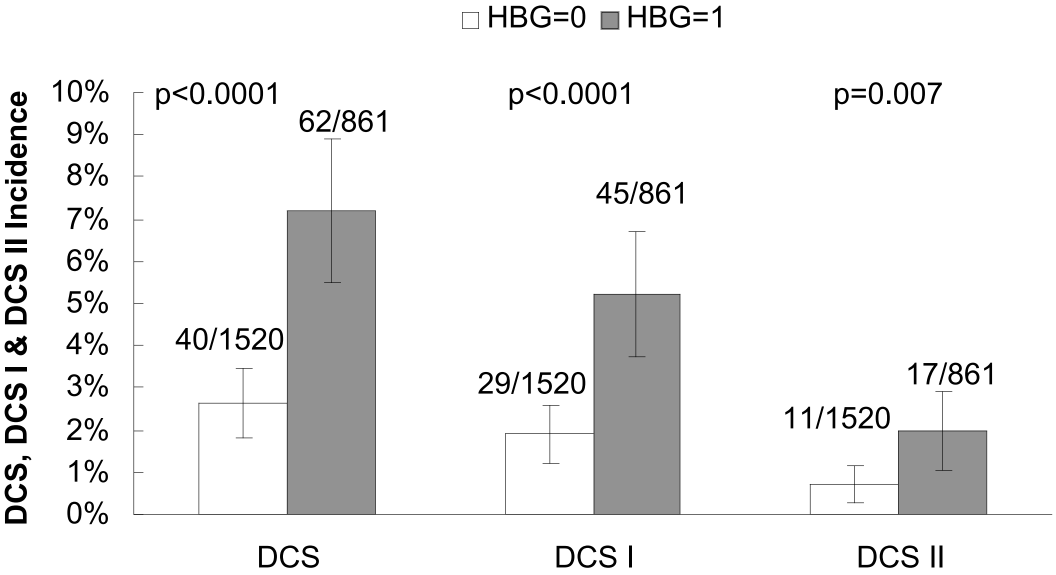

Figure 0: DCS incidence in Navy data listed by HBG. The number of DCS events and dives appears as a ratio over the 95% binomial confidence limits.

3.2 Mean Diver Characteristics

The mean values for age, height, weight, BMI, and percent body fat (where available) are listed in Table 11 for the entire data set, in Table 12 by inert gas, and in Table 13 by HBG outcome. The mean values of age, height, weight, BMI, and percent body fat corresponding to DCS incidents are listed in Table 14. Divers who used helium mixes were found to be slightly older, taller, and fatter, but with a lower BMI, than divers who used nitrogen mixes.

U.S. Navy	Number	Mean	Std Dev	Min	Max
Age (yrs)	2381	28.27	5.64	20.00	46.00
Height (m)	2381	1.79	0.06	1.58	2.01
Weight (kg)	2381	79.86	9.21	56.82	114.55
BMI (kg/m2)	2381	24.85	2.25	20.38	32.49
% Body fat	1898	15.22	5.52	3.60	31.20

Table 3: Mean diver characteristics for all dives in the Navy data.

U.S. Navy	Gas	Number	Mean	Std Dev	Min	Max	p-value
Age (yrs)	N_2	873	27.52	5.48	20.00	46.00	
	He	1508	28.71	5.68	20.00	44.00	<.0001
Height (m)	N_2	873	1.788	0.061	1.575	2.007	
	He	1508	1.794	0.059	1.575	2.007	0.0199
Weight (kg)	N_2	873	79.88	8.31	57.27	114.55	
	He	1508	79.85	9.69	56.82	113.64	0.9383
BMI (kg/m2)	N_2	873	24.99	2.18	20.40	32.47	
	He	1508	24.78	2.28	20.38	32.49	0.026
% Body fat	N_2	870	13.23	4.87	3.60	25.80	
	He	1028	16.90	5.48	4.60	31.20	<.0001

Table 3: Mean diver characteristics for the Navy data listed by inert gas used.

U.S. Navy	HBG	Number	Mean	Std Dev	Min	Max	p-value
Age (yrs)	0	1520	27.89	5.58	20.00	45.00	
	1	861	28.96	5.67	20.00	46.00	<.0001
Height (m)	0	1520	1.79	0.06	1.58	2.01	
	1	861	1.79	0.06	1.58	2.01	0.1166
Weight (kg)	0	1520	78.89	8.75	56.82	114.55	
	1	861	81.59	9.73	60.00	114.55	<.0001
BMI (kg/m2)	0	1520	24.60	2.19	20.38	32.49	
	1	861	25.30	2.28	20.38	32.49	<.0001
% Body fat	0	1287	14.61	5.35	3.60	29.40	
	1	611	16.50	5.67	4.20	31.20	<0.001

Table 3: Mean diver characteristics in Navy data listed by HBG outcome.

U.S. Navy	DCS	Number	Mean	Std Dev	Min	Max	p-value
Age (yrs)	DCS1	74	27.73	5.42	20.00	39.00	0.4101
	DCS2	28	29.32	5.28	21.00	40.00	0.3312
	not DCS	2279	28.28	5.65	20.00	46.00	
Height (m)	DCS1	74	1.79	0.06	1.60	1.93	0.8205
	DCS2	28	1.83	0.07	1.70	2.01	0.0015
	not DCS	2279	1.79	0.06	1.58	2.01	
Weight (kg)	DCS1	74	82.76	8.78	66.36	106.82	0.0051
	DCS2	28	84.38	9.78	70.00	99.09	0.0077
	not DCS	2279	79.72	9.19	56.82	114.55	
BMI (kg/m2)	DCS1	74	25.84	2.39	20.38	32.47	0.0001
	DCS2	28	25.21	1.92	21.05	28.84	0.3612
	not DCS	2279	24.82	2.24	20.38	32.49	
% Body fat	DCS1	67	15.96	5.48	4.80	26.00	0.2711
	DCS2	25	17.20	5.42	4.60	26.80	0.0793
	not DCS	1806	15.16	5.52	3.60	31.20	

Table 3: Mean diver characteristics listed by DCS outcome.

Age, weight, BMI, and percent body fat were found to be significantly associated with HBG outcome. Weight was significant for DCS I and DCS II outcomes. BMI was significant only for DCS I while height was significant only for DCS II. The association of uncontrolled diver characteristics with the outcome variables suggests that statistical control for diver characteristics should be applied.

3.3 HBG Models

Figure 10 and Tables 15 and 16 indicate that inert gas was significantly associated with HBG as determined by logistic regression. Similarly, the diver's age and BMI were significant predictors of a positive HBG outcome. The percent body fat of the diver was also a significant predictor of HBG when tested alone, but since it was not recorded for all divers, it was omitted from further analysis. The log likelihoods, c-indices, and odds ratios (with upper and lower confidence levels) for the empirical exposure and LEM exposure HBG models are shown in Tables 15 and 16. The ORs of significant variables are shown with changes for the continuous variables defined as follows: D1 per 10 ft, T1 and TDT per 10 min, PrT per 100 units, age per 5 years, weight per 5kg, height per meter, BMI per one unit, and cPDCS (cP) per percent. The Haldane tissue model was not capable of satisfactorily representing the exposure so their odds ratios and c-indices are not reported. The Haldane model was considered unsuccessful because the model failed to differentiate between helium and nitrogen inert gas solubility and HBG probability was represented to decrease with increasing P_t. The c-indices of the empirical exposure and LEM exposure HBG models are plotted in Figure 10 to give a visual comparison of models.

Figure 0: Comparison of empirical exposure and LEM exposure models of HBG by c-index, including significant ORs.

Model	- 2 LL	LL	c	PRT 100 units	Gas	age 5 yrs	bmi
Null	2942.07	-1471.04	0.5	~	~	~	~
Raw data gas	2892.14	-1446.07	0.57	~	1.97	~	~
exposure	2790.72	-1395.36	0.65	1.22	1.83	~	~
exposure +diver	2725.46	-1362.73	0.68	1.22	1.96	1.10	1.16
Exact	2625.88	-1312.94	1.0	~	~	~	~

Table 3: Results of empirical exposure model for HBG

Model	- 2 LL	LL	c	cP	Gas	age 5 yrs	bmi
Null	2942.07	-1471.04	0.5	~	~	~	~
Raw data gas	2892.91	-1446.46	0.57	~	1.97	~	~
cPDCS	2903.93	-1451.96	0.57	1.22		~	~
add gas	2860.11	-1430.06	0.61	1.21	1.91	~	~
add diver	2791.31	-1395.65	0.65	1.22	1.96	1.11	1.16
exact	2625.88	-1312.94	1.0	~	~	~	~

Table 3: Results of LEM exposure model for HBG

3.4 DCS Models

The empirical models of DCS all exhibited significant improvement when diver characteristics were added and improved again when HBG was added as a predictor (Figs. 11, 13, 15 and Tables 17, 19, 21). The models of the different types of DCS possessed different significant predictor variables. Gas was significant in all empirical models of DCS II, except when HBG was added. Gas only became significant when modeled with HBG for DCS I and was never significant in models of all DCS together. Physically, only BMI was significant for models of DCS I. In models of DCS II, BMI and weight were significant until HBG was added which made height the only significant characteristic. DCS had weight as the only significant characteristic until HBG was added to the model resulting in BMI and height becoming the significant characteristics. TDT was significant in all empirical exposure models except for when HBG was added to the DCS II model. The significant variables and their odds ratios for the empirical models can be found for each DCS outcome in Tables 17, 19, and 21. The Haldane tissue model for all types of DCS was again not able to satisfactorily represent the exposure, so their odds ratios are not reported. The graphical comparison of c-indices for the empirical exposure models of all DCS outcomes are displayed in Figures 11, 13, and 15.

The results for the LEM exposure models can be found for each outcome in Tables 18, 20, and 22. The LEM exposure models found the same significant diver characteristics as the empirical models for each outcome of DCS, except weight was the only significant characteristics for all DCS in the LEM model. Interestingly, gas is found to be a significant variable in the LEM exposure models, although the model theoretically takes gas into account. The models show the risk of DCS and DCS I are greater when nitrogen mixes are used, as seen in the raw data. An interaction between inert gas and the cPDCS variable was found in the LEM models for DCS II, it was the only interaction that occurred. The inert gas-cPDCS interaction was significant in the DCS II models until HBG was introduced as a predictor variable. The graphical comparison of c-indices for the LEM models of all DCS outcomes are displayed in Figures 12, 14, and 16. When a significant interaction exists, an odds ratio can no longer be computed, denoted by an x.

Model	- 2 LL	LL	c	D1 10 ft	T1 10 min	PRT 100 units	TDT 10 min	Gas	HBG	Wt 5 kg	bmi	Ht m
Null	784.3	-392.1	0.5	~	~	~	~	~	~	~	~	~
Raw data (gas)	779.8	-389.9	0.55	~	~	~	~	0.63	~	~	~	~
Raw data (hbg)	762.6	-381.3	0.62	~	~	~	~	~	2.68	~	~	~
exposure	760.9	-380.5	0.61	0.89	0.91	ns	1.04	ns	~	~	~	~
exp + diver	746.9	-373.4	0.68	0.88	0.91	ns	1.08	ns	~	1.2	ns	ns
exp + diver + HBG	727.6	-363.8	0.72	0.95	ns	0.90	1.07	ns	2.88	ns	1.1	34.5
Exact	593.2	-296.6	1.0	~	~	~	~	~	~	~	~	~

Table 4: Results of empirical exposure model of DCS.

Model	- 2 LL	LL	c	cP	Gas	HBG	Wt 5kg
Null	784.3	-392.1	0.5	~	~	~	~
Raw data gas	779.8	-389.9	0.55	~	0.63	~	~

raw data HBG	762.6	-381.3	0.62	~	~	2.68	~
cPDCS	773.3	-386.6	0.60	1.30	~	~	~
add gas	767.6	-383.8	0.61	1.31	0.60	~	~
add diver	753.0	-376.5	0.66	1.33	0.58	~	1.23
add HBG	735.8	-367.9	0.70	1.27	0.50	2.50	1.19
exact	593.2	-296.6	1.0	~	~	~	~

Table 5: Results of LEM exposure model of DCS

Figure 0: Comparison of empirical exposure models of DCS by c-index, including significant ORs.

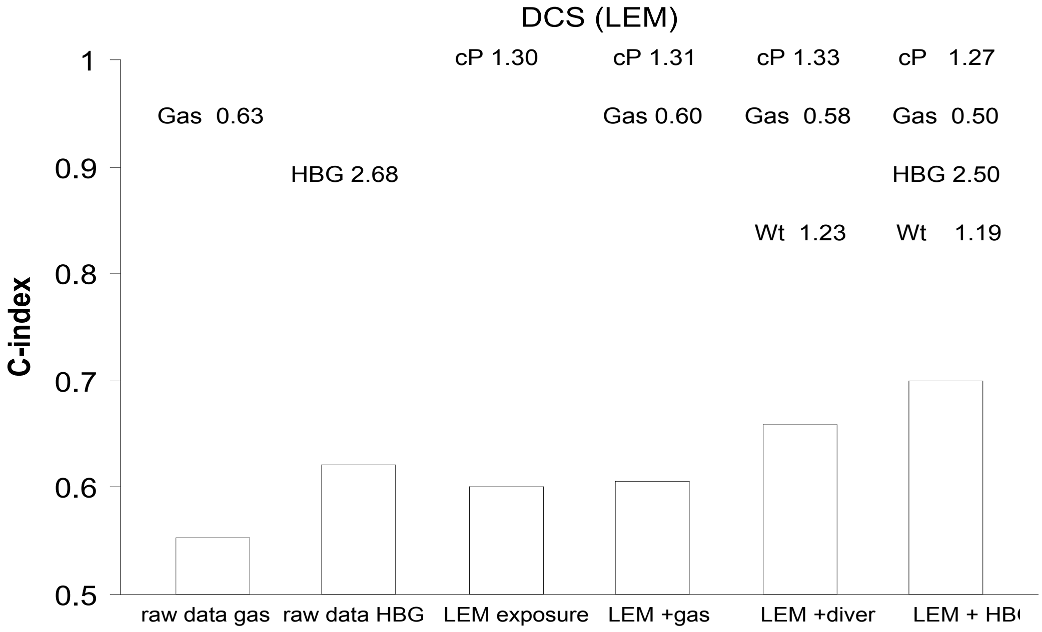

Figure 0: Comparison of LEM exposure models of DCS by c-index, including significant ORs.

Model	- 2 LL	LL	c	PRT 100 units	D1 10 ft	TDT 10 min	Gas	HBG	bmi
Null	599.1	-299.5	0.5	~	~	~	~	~	~
Raw data gas	590.2	-295.1	0.59	~	~	~	0.47	~	~
Raw data HBG	583.4	-291.7	0.62	~	~	~	~	2.70	~
exposure	585.9	-293.0	0.59	ns	0.94	1.06	ns	~	~
add diver	575.8	-287.9	0.68	ns	0.94	1.06	ns	~	1.19
add HBG	556.4	-278.2	0.73	0.90	ns	1.05	0.55	3.08	1.14
exact	429.7	-214.9	1.0	~	~	~	~	~	~

Table 6: Results of empirical exposure model of DCS I.

Model	- 2 LL	LL	c	cP	Gas	HBG	bmi
Null	599.1	-299.5	0.5	~	~	~	~
Raw data gas	590.2	-295.1	0.59	~	0.47	~	~
Raw data HBG	583.4	-291.7	0.62	~	~	2.70	~
cPDCS	593.6	-296.8	0.59	1.24	~	~	~
add gas	583.6	-291.8	0.62	1.27	0.45	~	~
add diver	573.6	-286.8	0.67	1.27	0.46	~	1.19
add hbg	559.6	-279.8	0.71	1.21	0.39	2.66	1.15
exact	429.7	-214.9	1.0	~	~	~	~

Table 7: Results of LEM exposure model of DCS I.

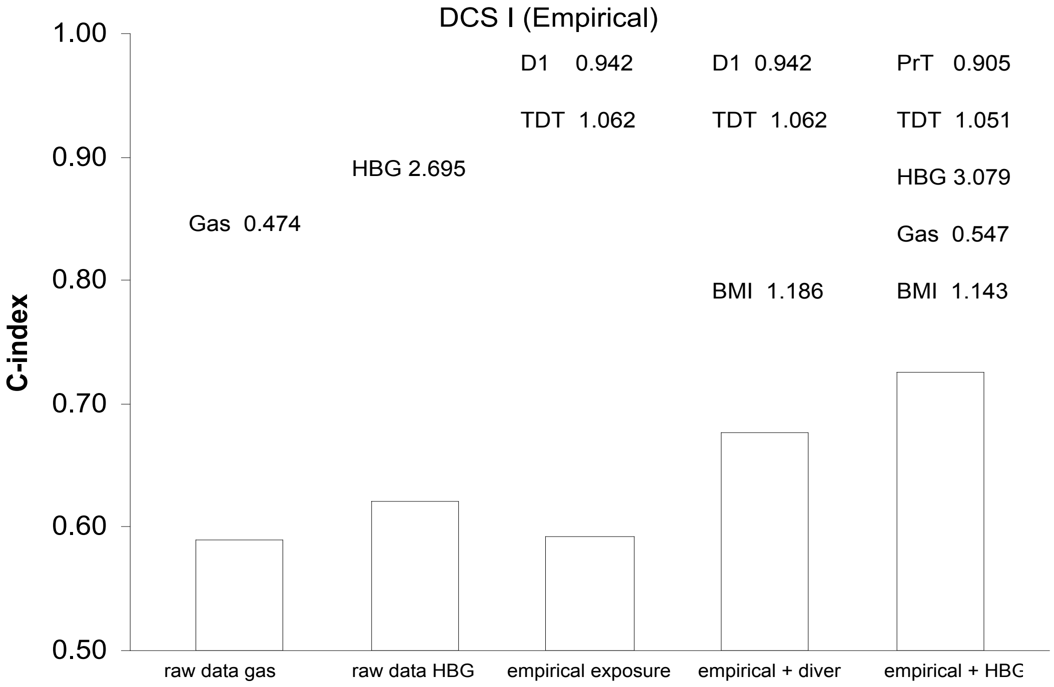

Figure 0: Comparison of empirical exposure models of DCS I by c-index, including significant ORs.

Figure 0: Comparison of LEM exposure models of DCS I by c-index, including significant ORs.

Model	- 2 LL	LL	c	D1 10 ft	TDT 10 min	Gas	HBG	Wt 5 kg	BMI	Ht m
null	298.7	-149.4	0.5	~	~	~	~	~	~	~
Raw data HBG	292.3	-146.1	0.62	~	~	~	2.64	~	~	~
exposure	288.2	-144.1	0.67	0.99	1.01	3.42	~	~	~	~
add diver	277.0	-138.5	0.75	0.99	1.01	3.22	~	1.12	0.71	ns
add HBG	282.5	-141.3	0.70	ns	ns	ns	2.57	ns	ns	>999
exact	214.3	-107.1	1.0	~	~	~	~	~	~	~

Table 8: Results of empirical exposure model of DCS II.

Model	- 2 LL	LL	c	cP	Gas	cP*gas	HBG	Ht m	Wt 5kg	BMI
null	298.7	-149.4	0.5	~	~	~	~	~	~	~
Raw data HBG	292.3	-146.1	0.62	~	~	~	2.64	~	~	~
cPDCS	292.0	-146.0	0.63	1.46	~	~	~	~	~	~
gas interaction	285.4	-142.7	0.67	x	x	x	~	~	~	~
diver w/ gas inter	273.3	-136.6	0.75	x	x	x	~	ns	1.13	0.71
add HBG	276.5	-138.3	0.74	1.45	ns	ns	2.31	>999	~	~
exact	214.3	-107.1	1.0	~	~	~	~	~	~	~

Table 9: Results of LEM exposure model of DCS II.

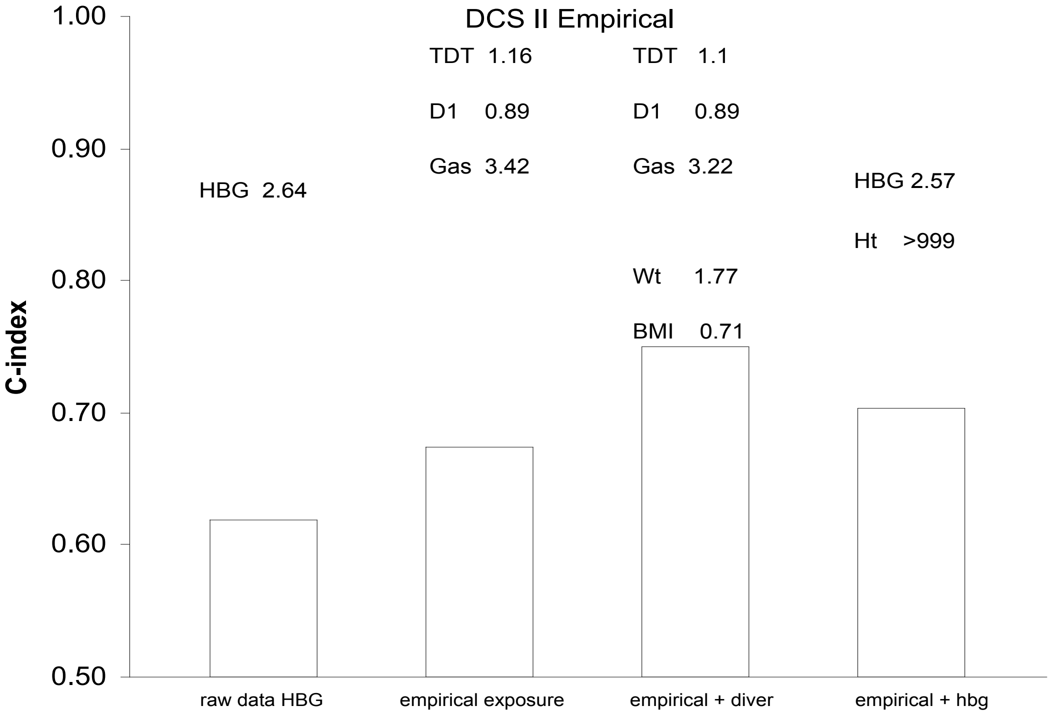

Figure 0: Comparison of empirical and PDCS models of DCS II by c-index, including significant ORs.

4 Discussion

4.1 Comparison of Duke to Navy Data

The observation of increased HBG incidence with helium breathing mixes found in the Duke study was confirmed in the larger Navy data set. A side-by-side comparison of HBG incidence by inert gas is found in Figure 17. HBG were nearly twice as common in the Navy study as in the Duke study. This difference may have been due to differences in Doppler signal interpretation or due to more stressful dives.

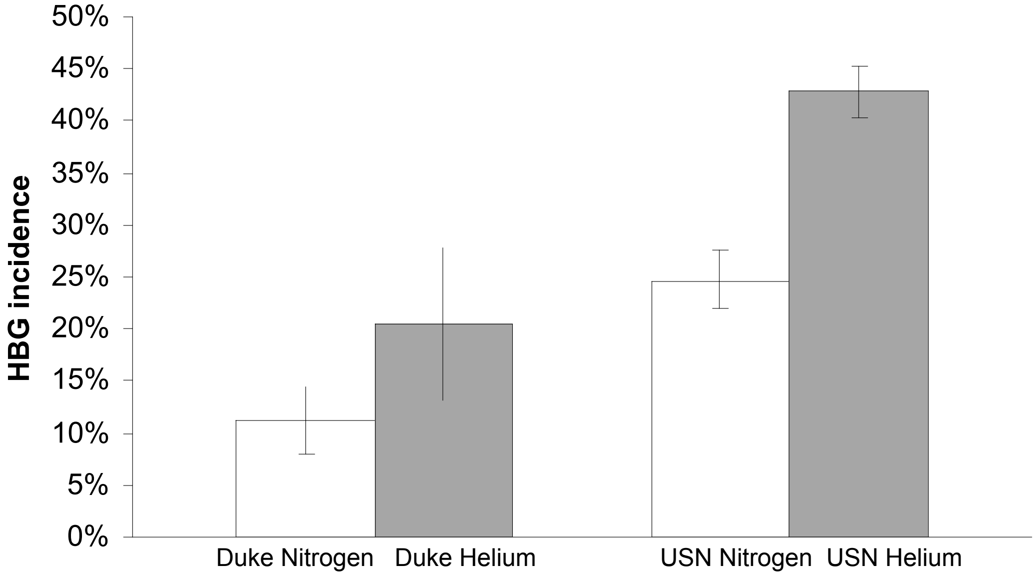

Figure 0: Comparison of HBG incidence in Duke and Navy data listed by inert gas.

The differences between He and N_2 in the incidences of all DCS and DCS I was not significant in the smaller Duke study, but both DCS and DCS I had significantly lower incidences with He and N_2 in the larger Navy study. The incidence of DCS II was greater with He in both the Duke study and Navy data, but this difference was only significant for the Duke data. The side-by-side comparison of DCS incidence by inert gas for both studies is illustrated in Figure 18.

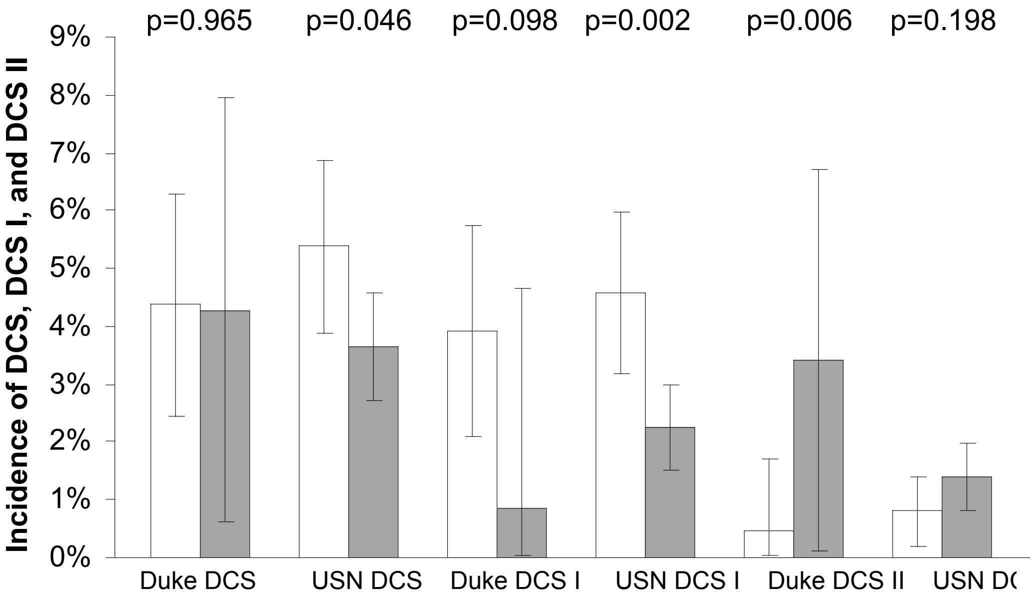

Figure 0: Comparison of DCS incidence in Duke and Navy data listed by inert gas.

HBG was significantly associated with all DCS outcomes. The side-by-side comparison of HBG in relation to the DCS outcomes of the Duke and Navy data is illustrated in Figure 19.

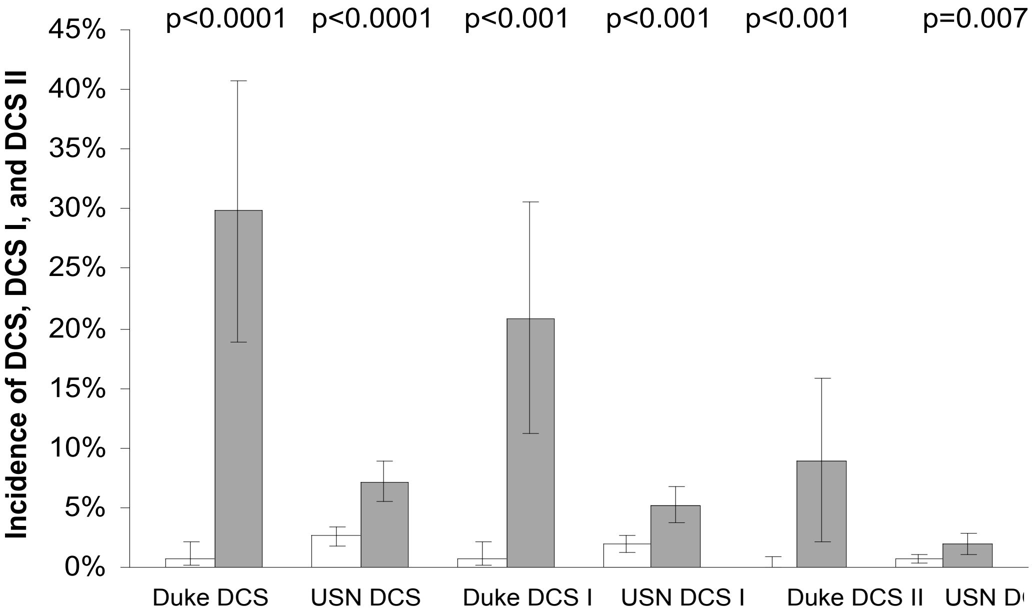

Figure 0: Comparison of DCS incidence in Duke and Navy data listed by HBG.

4.2 Controls for Exposure and Diver

The outcome models presented in Results included only those predictor variables that were statistically significant. Such an approach provides the simplest (most parsimonious) models but makes it difficult to compare and contrast models. To facilitate model comparison, all the exposure and diver variables that were significant at least once in the earlier models were entered into the same model and used to predict all the outcome variables. Table 23 presents the results of this analysis. This approach had an additional advantage of rejecting variables for which significance was marginal or possibly invalid. For example, age was the only diver characteristic to remain significant and only in models of HBG. Age has been found to be a significant factor for VGE in recreational diving (Dunford et al., 2003).

Three methods were used to control for exposure severity. The first used the empirically observed exposure characteristics (inert gas, D1, T1, PrT, and TDT) and fit the Navy data well, possessing the lowest likelihoods of the three methods, but as it is data-specific, it was not well suited for generalization to other dives. While the HBG incidence increased with PrT, the odds ratios for the DCS models suggested that the dives became less risky as depth and PrT increased and more risky as total decompression time (TDT) increased. This may have indicated that the dive profiles selected for testing became more conservative with increasing depth and time, while TDT was longer for the dives judged as “risky.”

The second method of controlling for exposure severity used the inert gas tension in a Haldane tissue compartment on the surface at the end of the dive. This method was unsuccessful as it was either computationally unstable during parameter optimization or it predicted decreased risk of HBG with increasing tissue tension in opposition to the model