Computers in Biology and Medicine 86 (2017) 55–64

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/compbiomed

Probabilistic pharmacokinetic models of decompression sickness in humans, part 1: Coupled perfusion-limited compartments

F. Gregory Murphy [a, b], Ethan A. Hada [c], David J. Doolette [b, d], Laurens E. Howle [a, e, f, *]

[a] Mechanical Engineering and Materials Science Department, Duke University, Durham, NC, USA
[b] Navy Experimental Diving Unit, Panama City, FL, USA
[c] The Henry M. Jackson Foundation, Bethesda, MD, USA
[d] Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA
[e] Department of Radiology, Duke University Medical Center, Durham, NC, USA
[f] BelleQuant Engineering, PLLC, Mebane, NC, USA

ARTICLE INFO

Keywords:
Pharmacokinetics
Scuba diving
Hyperbarics
Nitrogen
Inert gas supersaturation
Decompression sickness
Decompression illness

ABSTRACT

Decompression sickness (DCS) is a disease caused by gas bubbles forming in body tissues following a reduction in ambient pressure, such as occurs in scuba diving. Probabilistic models for quantifying the risk of DCS are typically composed of a collection of independent, perfusion-limited theoretical tissue compartments which describe gas content or bubble volume within these compartments. It has been previously shown that 'pharmacokinetic' gas content models, with compartments coupled in series, show promise as predictors of the incidence of DCS. The mechanism of coupling can be through perfusion or diffusion. This work examines the application of five novel pharmacokinetic structures with compartments coupled by perfusion to the prediction of the probability and time of onset of DCS in humans. We optimize these models against a training set of human dive trial data consisting of 4335 exposures with 223 DCS cases. Further, we examine the extrapolation quality of the models on an additional set of human dive trial data consisting of 3140 exposures with 147 DCS cases. We find that pharmacokinetic models describe the incidence of DCS for single air bounce dives better than a single-compartment, perfusion-limited model. We further find the U.S. Navy LEM-NMRI98 is a better predictor of DCS risk for the entire training set than any of our pharmacokinetic models. However, one of the pharmacokinetic models we consider, the CS2T3 model, is a better predictor of DCS risk for single air bounce dives and oxygen decompression dives. Additionally, we find that LEM-NMRI98 outperforms CS2T3 on the extrapolation data.

1. Introduction

Decompression sickness (DCS) is thought to result from bubbles which form when a state of gas supersaturation occurs in tissue [1,2]. During an exposure to a hyperbaric environment, such as during an underwater, compressed gas dive, inert gases from the breathing mixture (typically nitrogen or helium) are dissolved into tissues at increased pressure. Gas supersaturation, and bubble nucleation, can occur upon ascent (decompression). The risk of DCS is controlled by following decompression schedules that specify the time at depth and the rate of ascent. Probabilistic models of gas content and/or bubble growth in theoretical tissue compartments have been successfully used to predict the incidence of DCS associated with a given diving exposure and to produce decompression schedules [3–7].

Probabilistic methods of predicting the probability and time of onset of DCS typically rely upon a collection of compartments to model the gas content and/or bubble growth associated with DCS. These compartments are mathematical abstractions meant to simulate the different rates of gas uptake and elimination found in various tissues of the body, but do not represent actual tissues. The calculated gas supersaturation or bubble volume within a compartment is then converted via a risk function into a probability that DCS will occur for a given exposure [3]. Commonly, decompression models use a collection of independent (or "parallel") perfusion-limited compartments, each notionally perfused with arterial blood and with no transfer of gas between compartments. Pharmacokinetic and pharmacodynamic models similarly use theoretical tissue compartments to simulate the uptake and action of drugs, but commonly have structures where compartments are coupled such that transfer occurs between compartments. We refer to decompression models with coupled compartments as 'pharmacokinetic gas content models'.

* Corresponding author. Mechanical Engineering and Materials Science Department, Duke University, Durham, NC, 27708-0300, USA.
E-mail address: laurens.howle@duke.edu (L.E. Howle).

http://dx.doi.org/10.1016/j.compbiomed.2017.04.014
Received 21 January 2017; Received in revised form 17 April 2017; Accepted 23 April 2017

Pharmacokinetic gas content models have some potential advantages over parallel perfusion-limited models. First, it has been shown that pharmacokinetic gas content models more accurately describe the uptake and washout of nitrogen and helium in the skeletal muscle and cerebral tissue of sheep than do single perfusion-limited compartments [8,9]. This more physiologically-relevant description of inert gas kinetics might improve decompression model fidelity. Second, most parallel perfusion-limited probabilistic models share the property that the hazard is highest, and the bulk of the risk is accumulated, immediately after decompression [10]. In practice however, DCS typically onsets many minutes or hours after decompression [11,12]. Pharmacokinetic models have the potential to delay risk accumulation [13]. Third, pharmacokinetic gas content models calibrated with a circumscribed data set have been reported as superior to parallel perfusion-limited models for predicting the incidence only of decompression sickness associated with saturation drop out events [14]. This superior performance of the pharmacokinetic models has been attributed to their coupled compartment structure [14]. However, when calibrated with similar data sets, parallel compartment and pharmacokinetic gas content models similarly predict the DCS incidence associated with saturation drop out dives [15]. Therefore, it is possible that training the models to a much smaller and more specific data than the broad data sets generally used for model calibration imparted the favorable behavior. Also, pharmacokinetic gas content models have been reported to predict the probability of DCS better for low-risk dives for which parallel models tend to over-predict DCS risk [14,16].

Motivated by these potential advantages, we explore the applicability of pharmacokinetic gas content models for predicting the occurrence and time of onset of DCS in humans using the large and diverse NMRI98 data set [5]. Whereas there are successful models of time of onset of DCS with conventional independent compartment structure, most previously-reported pharmacokinetic gas content models have been models of DCS occurrence only. In this work, we calibrate models with the time of onset information in the NMRI98 data set using the methods introduced into the field of probabilistic DCS modeling by Weathersby *et al* [10]. Fitting decompression models to the additional information embodied in time of onset provides a greater challenge which can uncover model deficiencies not evident when fit to DCS occurrence only. Previously reported pharmacokinetic gas content models have been mammillary models or serially-coupled compartments with gas exchange notionally by diffusion. The pharmacokinetic gas content models investigated in this report have serial and/or cyclic structures and notional gas exchange is by perfusion.

2. Material and methods

All models were programmed in C# using a previously described computational system [17] with parameter values were determined using the Nelder-Mead algorithm to optimize the log likelihood against the NMRI98 U.S. Navy dive data set [5]. The time to find best fit solutions was reduced by directly calculating the optimal gain [18]. For each model, we obtained at least 32 optimized parameter sets and selected the set with the greatest log likelihood for comparison to other models. Each set of starting parameters was randomly drawn from normal distributions specifically tuned to each parameter. The general process of using maximum likelihood and survival analysis to optimize a gas content model has been previously described in the literature [19]. While recent work has explored the utility of Bayesian Inference for fitting probabilistic decompression models [20], we used log likelihood maximization for the present study due to the increased computational cost of the Bayesian method.

2.1. Data

The NMRI98 data set is composed of air and N_2-O_2 dives including bounce dives, repetitive dives, dives using oxygen to accelerate decompression, submarine escape dives, and saturation dives [5]. These data are summarized in Table 1. This data set is a subset of the U.S. Navy N_2-O_2 primary dive data set described by Temple *et al* [21]. The NMRI98 data has been described in multiple publications [5,21,22]. No institutional review board approval was required to use these de-identified data. All exposures in this data set were conducted in hyperbaric chambers; some dry and some wet. Depth and temperature were tightly controlled with the outcome of the exposure determined by medical officers from the institution that performed the dive trial. Each profile is recorded as a series of nodes, with each node being comprised of time, pressure, and inspired gas information. In addition to the nodes, each profile specifies how many exposures were recorded using that profile. For each DCS event, the last known time the subject was without manifestations of DCS and the first known time the subject had manifestations of DCS are recorded. The total number of exposures is 4335 across 1304 unique profiles, during which 223 cases of DCS occurred. Marginal DCS, which are manifestations thought to be related to decompression but considered to not require treatment with hyperbaric oxygen, were also recorded. Recent work has shown that marginal DCS events unfairly bias the model fit toward prediction of the outcome of saturation dives [23]. Therefore, we treated marginal DCS as non-events. In addition to the full data set, we also fit the models against the eight subsets separating the data by the exposure types of single air, single non-air, repetitive and multilevel air, repetitive and multilevel non-air, surface decompression with oxygen, oxygen decompression, and saturation, as shown in Table 1.

A separate subset of data was selected from the U.S.Navy N_2-O_2 primary dive data collection for use in testing a model's ability to extrapolate outside of its training set [21,24]. The extrapolation data set contained 3140 exposures distributed among 1198 profiles. During these exposures, 147 full DCS incidents occurred. Table 2 provides a breakdown of the extrapolation data by dive type along with the number of profiles, exposures, and the number of DCS cases associated with each data file. The extrapolation data were selected based upon availability and, consequently, not all dive data types are represented in the extrapolation data set.

2.2. Models

We derived six pharmacokinetic gas content models using the physical law of conservation of mass. These six models were then programmed and optimized against the U.S. Navy data set. Five of the models were novel PK structures and one was selected based upon its common use as a building block for more complex models. The Perfusion Limited Base Model (PLB) which consists of a single, perfusion-limited compartment is the most basic structure we explored and is the building block of many models currently in use by the U.S. Navy [4–6,25,26]. Three copies of our PLB in parallel but each with different parameters are equivalent to the well-studied EE1 model [25,26]. The pharmacokinetic gas content models were derived as a collection of well-stirred compartments with exponential gas uptake and elimination in each

Table 1
Dive data subset descriptions, number of profiles, exposures and the resulting number of observed DCS cases in the model training data. Note that marginal DCS incidents were considered to be non-events for this work [23]. The All Minus Saturation category consists of all data less the Saturation data.

Subset Name	Number of Profiles	Number of Exposures	Number of DCS Cases
Single Air	373	1005	53
Single Non-Air	264	678	25
Repetitive and Multilevel Air	126	565	34
Repetitive and Multilevel Non-Air	100	607	26
Surface Decompression with Oxygen	82	427	11
Oxygen Decompression	184	586	22
Saturation	175	467	52
Total	***1304***	***4335***	***223***
All Minus Saturation	1129	3868	171