Calibration of a bubble evolution model to observed bubble incidence in divers

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Gault KA, Tikuisis P, Nishi RY. Calibration of a bubble evolution model to observed bubble incidence in divers. Undersea Hyperbaric Med 1995; 22(3):249–262.—The method of maximum likelihood was used to calibrate a probabilistic bubble evolution model against data of bubbles detected in divers. These data were obtained from a diverse set of 2,064 chamber man-dives involving air and heliox with and without oxygen decompression. Bubbles were measured with Doppler ultrasound and graded according to the Kisman–Masurel code from which a single maximum bubble grade (BG) per diver was compared to the maximum bubble radius ($R_{\text{max}}$) predicted by the model. This comparison was accomplished using multinomial statistics by relating BG to $R_{\text{max}}$ through a series of probability functions. The model predicted the formation of the bubble according to the critical radius concept and its evolution was predicted by assuming a linear rate of inert gas exchange across the bubble boundary. Gas exchange between the model compartment and blood was assumed to be perfusion-limited. The most successful calibration of the model was found using a trinomial grouping of BG according to no bubbles, low, and high bubble activity, and by assuming a single tissue compartment. Parameter estimations converge to a tissue volume of 0.00036 cm$^3$, a surface tension of 5.0 dyne·cm$^{-1}$, respective time constants of 27.9 and 9.3 min for nitrogen and helium, and respective Ostwald tissue solubilities of 0.0438 and 0.0096. Although not part of the calibration algorithm, the predicted evolution of bubble size compares reasonably well with the temporal recordings of BGs.

diving, maximum likelihood, Doppler, bubble grades, prediction model

It is generally accepted that bubbles lead to decompression sickness (DCS) (1), but little is known about their process of evolution in human tissue (2). The condition of inert gas supersaturation, which is a prerequisite for bubble formation, became the basis of early predictive models for the occurrence of DCS (3,4). However, greater consideration to the formation and growth of bubbles has been given to more recent model developments (5,6). While these models are intuitively correct and supported empirically, a certain amount of
inference is involved in the connection between bubble formation and DCS. This uncertainty was the prime motivation in an earlier study (7) for testing certain bubble models against data that measured the presence of bubbles directly.

Since bubbles are good scatterers of ultrasound they can be detected in the blood circulation using Doppler ultrasound. The quantity of bubbles observed correlates well with the severity or stress of decompression (8–12), and because bubble events occur far more frequently than DCS, fewer dives are required to judge the relative severity of decompression. In the earlier study (7), venous gas emboli in divers were detected using Doppler ultrasound and the maximum recorded bubble scores were related to the maximum gas volume that potentially could be liberated during decompression. Since then, the prediction models for DCS have been refined to include the kinetics of bubble formation and growth.

Another improvement over the earlier study concerns the association between the prediction of bubble events and bubble grades (BGs) based on Doppler measurements. Previously, the BG scale used was analogous to the classification of DCS incidence, that is, bubble outcome was assigned a value of 0 for no bubbles or low BG, 0.5 for intermediate BG, and 1 for high BG using a modified binomial distribution (where the intermediate outcome is treated as a simple combination of the binomial outcomes of 0 and 1). A more rigorous approach is to allow a continuous range of probabilities through the application of multinomial statistics where the intermediate outcomes are treated independently of the other outcomes. This approach, in addition to the application of bubble kinetics, has been undertaken in the present study to model in vivo bubble evolution.

The aim of this study, therefore, is to develop a bubble model that can be used to predict the outcome of BG, while adhering as closely as possible to the physical and physiologic processes in the human body. Bubble formation will be based on the critical radius concept (13) which states that for a fixed gas content, temperature, and tissue volume there exists a drop in ambient pressure for which a bubble, if formed, would be in equilibrium with its surroundings. Gas exchange between the bubble and the tissue assumes a linear rate dependency, and gas exchange between the tissue and blood assumes perfusion limitation. The method of maximum likelihood is then used to fit the model parameters to BG data collected at the Defence and Civil Institute of Environmental Medicine (DCIEM) from experimental chamber dives.

THEORETICAL DEVELOPMENT

Divers exhibiting large BGs are found to be more likely to develop DCS than those who exhibit lower BGs (8,9). The presence of bubbles in the blood stream is also thought to be indicative of bubbles elsewhere in the body (10). Although it is not known where bubbles originate, it is reasonable to simulate their evolution in compartments having tissue-like characteristics. In this study, a semi-closed, tissue-based bubble model will be developed for the prediction of BG assuming a direct correspondence with bubbles detected in the circulatory system. Table 1 provides a glossary of terms used in this development.

**Bubble formation**

Upon formation, the bubble is assumed to be in a state of equilibrium (13,14) and its size, defined by the critical radius \( R_c \), is obtained through the following mass balance (7):

\[
L_tP_tV = L_cP_cV + \frac{4}{3} \pi R_c^3 P_t^i
\]
Table 1: Glossary

- $a, b$: probability function parameters
- $BG$: bubble grade
- $C_i$: concentration of gas $i$
- $f_i$: fraction of gas $i$ in bubble
- $J_i$: gas flux of gas $i$ between bubble and tissue
- $k_B$: Boltzmann gas constant
- $k_i^L$: linear rate constant of gas flux of gas $i$
- $L, LL$: likelihood, log-likelihood function
- $L_i$: Ostwald solubility of gas $i$
- $N_i$: total gas content of gas $i$
- $N_i$: number of molecules of gas $i$ in bubble
- $P_i^B$: ambient pressure
- $P_i$: vapor pressure
- $P_i^T$: gas tension of gas $i$ in tissue
- $P_i^B$: gas tension of gas $i$ in blood
- $P_i$: gas pressure of gas $i$ in bubble
- $P_r$: probability function
- $Q$: blood perfusion of tissue
- $R$: bubble radius
- $R_c$: critical radius of liquid-gas solution
- $R_{max}$: maximum predicted bubble radius
- $T$: tissue temperature
- $V$: tissue volume
- $\gamma$: surface tension
- $\tau_i$: time constant of gas $i$

where $L_i$ is the Ostwald solubility of gas $i$ in the tissue, $P_i$ is the initial tissue tension of gas $i$, $P_i^T$ is the pressure of gas $i$ in the bubble, and $V$ is the tissue volume. The left side of the equation is a measure of the gas content in the tissue before the bubble is formed, and the right side is the sum of the remaining gas dissolved in tissue and of gas in the bubble after its formation.

The internal gas pressures of a bubble containing nitrogen (gas 1), helium (gas 2), and water vapor ($P_v$; assumed constant) can be expressed in terms of the ambient pressure ($P_{amb}$) and the Laplace surface tension ($\gamma$) (15):

$$P_i^T + P_i^B = P_{amb} + \frac{2\gamma}{R} - P_i$$ (2)

If $R$ is set equal to $R_c$, then Eq. 1 can be combined with Eq. 2 to obtain the following $7^{th}$ order polynomial:

$$R_c^7 \cdot \frac{16\pi^2 (P_{amb} - P_v)}{9V^2L_1L_2} + R_c^6 \cdot \frac{32\pi^2 \gamma}{9V^2L_1L_2}
+ R_c^5 \cdot \frac{4\pi}{3V} \left[ (P_{amb} - P_v) \left( \frac{1}{L_1} + \frac{1}{L_2} \right) - \left( \frac{P_1}{L_1} + \frac{P_2}{L_2} \right) \right]
+ R_c^4 \cdot \frac{8\pi \gamma}{3V} \left( \frac{1}{L_1} + \frac{1}{L_2} \right) + R_c \cdot (P_{amb} - P_v - P_1 - P_2) + 2\gamma = 0$$ (3)
where
\[ P_i = \frac{N_i k_B T}{L_i V} \]  
and where \( N_i \) is the total gas content, \( k_B \) is the Boltzmann gas constant, and \( T \) is the tissue temperature (assumed to be 37°C in this study).

At the instant when gas supersaturation of the tissue first occurs there are no positive real roots to Eq. 3, indicating that if bubble nucleation took place the bubble would dissolve. Upon a sufficient reduction in the ambient pressure, Eq. 3 will have two positive but unequal real roots, one that represents a stable equilibrium state and the other that represents an unstable equilibrium state (13, 14). At a unique intermediate ambient pressure a point is reached at which there is only one positive real root. This represents the metastable equilibrium state (\( R_c = R_m \)) since a bubble in this state is stable against growth but unstable against dissolution. If the conditions for the metastable state are met and a bubble does not yet exist, then a bubble is assumed to form with \( R = R_m \).

**Bubble gas exchange**

Gas exchange between the bubble and the tissue is assumed to be linearly dependent on the concentration difference across the bubble boundary with no interaction between different gases (14):
\[ J_i = k_i^t \cdot \Delta C_i \]  
where \( J_i, k_i^t, \) and \( C_i \) are the gas flux, linear rate constant (related to gas diffusivity (16)), and the concentration difference between gas \( i \) in the bubble and that in the tissue, respectively. The change in the number of gas molecules in the bubble (\( N_i^b \)) is proportional to the surface area of the bubble multiplied by the gas flux:
\[ \frac{dN_i^b}{dt} = k_i^t 4\pi R^2 \cdot \left[ C_i^s \cdot f_i \cdot \left( 1 - \frac{P_i}{P_{amb}} + \frac{2\gamma}{RP_{amb}} \right) - C_i \right] \]  
where \( C_i^s \) is the saturation concentration of gas \( i \) in the tissue defined by:
\[ C_i^s = \frac{L_i}{k_B T} \cdot P_{amb} \]  
and where \( f_i \) is the fraction of gas \( i \) in the bubble.

**Tissue gas exchange**

Gas exchange between the tissue and blood is modeled according to blood perfusion limitation (3):
\[ \frac{dP_i}{dt} = \frac{P_i^b - P_i}{\tau_i} \]  
where \( P_i^b \) is the gas tension in the blood and \( \tau_i \) is the time constant related to the blood perfusion (\( Q \)) according to Hills (17):
BUBBLE EVOLUTION MODEL

\[ \frac{l}{\tau_i} = \frac{L_{i}^{m}}{L_{i}} \cdot Q \]

(9)

Blood flow is independent of the two inert gases and thus the resultant four gas solubilities (one for each gas, helium and nitrogen, and for blood and tissue) and two time constants are not independent. That is, \( \tau_{N_2} \) can be written in terms of \( \tau_{N_2} \) as:

\[ \tau_{He} = 1.52 \cdot \frac{L_{He}}{L_{N_2}} \cdot \tau_{N_2} \]

(10)

where the value of 1.52 is the nitrogen:helium ratio of gas solubilities in blood [using respective values of 0.0158 and 0.0104 (18)]. This reduces the number of estimated parameters to three, i.e., \( \tau_{N_2}, L_{N_2}, \) and \( L_{He} \).

Bubble evolution

Once the conditions for bubble formation have been satisfied through the use of Eq. 3, the following numerical procedure is repeated until the bubble’s maximum size has been determined:

1) increment time and adjust ambient pressure according to the dive profile;
2) calculate changes in bubble size and tissue gas tensions according to gas flux across the bubble boundary through Eq. 6;
3) calculate changes in the tissue inert gas tensions according to the tissue/blood gas exchange through Eq. 8; and
4) adjust bubble size for a change in the hydrostatic pressure according to Boyles’ law.

The following conditions must all be met to end the numerical computation when a bubble is present: 1) the bubble is less than 95% of its maximum size for the given dive profile, 2) its radius is shrinking, and 3) the diver is at surface. These conditions were chosen to reduce computational time because only the maximum bubble radius is required for this study. If the conditions for bubble formation have not been met either during decompression or during the initial period at surface following a change in the breathing gas composition, then the numerical computation is ended.

Simulations were conducted using one or two model compartments. When two compartments were used, their volume and surface tension values were the same whereas their time constants, gas solubilities, and gas exchange rates were different for each inert gas. The maximum bubble size from the two compartments was used for the prediction of BG.

DATA

Primary dive data for calibrating the model were obtained from experimental chamber dives conducted at DCIEM (19,20). These data comprised 362 profiles involving a total of 2,064 mandives as summarized in Table 2. Air dives consisted of single and repetitive exposures including no-stop dives, standard air decompression dives, dives with oxygen decompression at 9 meters of sea water (msw), and surface decompression dives involving surfacing from 9 msw and recompressing back to 12 msw to complete the decompression. Heliox dives were mostly 84% He:16% O\(_2\) with air decompression to 9 msw followed by O\(_2\) decompression at 9 msw. Bottom time began when the diver left the surface and ended when decompression began.

Bubble events were recorded using Doppler ultrasound (21,22) at the precordium, left
subclavian, and right subclavian sites of the diver’s body during both rest and after movement. The bubble observations began either during a decompression stop or after surfacing and were continued every 30–40 min thereafter for a minimum of 2 h until either the bubbles disappeared or diminished to a low count. The Kisman–Masurel Code (10,23,24) was used to classify bubbles in a single BG from 0 to 4 indicating no bubbles to maximum bubble activity. The maximum recorded BGs for the entire data set were 0 for 42.5% of the divers, 1 or 2 for 28.1%, and 3 or 4 for the remaining 29.4%. Greater details on the data used can be found in Gault (25).

Additional dive profiles were subsequently used to test the predictive power of the best-fitting model. These profiles, detailed in Results, included a number of dives on air and heliox to 45 msw for 30 min bottom time and a shallow air saturation dive to 15 msw.

**ANALYSIS**

The method of maximum likelihood (26) was applied in fitting the data of BG outcome to the maximum bubble size predicted by the model. The greater the number of BG classifications required for prediction, the greater the amount of data required for reasonable resolution of the model parameters. To obtain an acceptable distinction, the BGs were split into three groups, 0, \{1,2\}, and \{3,4\}, to represent no bubbles, low, and high bubble activity.

The likelihood function \(L\) for a trinomial outcome as defined above is given by:

\[
L = Pr_1^{m_1} \cdot Pr_2^{m_2} \cdot Pr_3^{m_3}
\]

where \(Pr_j\) is the probability of an occurrence of a given event \(j\) (note that \(Pr_3 = 1 - Pr_1 - Pr_2\)) and the superscript \(m_j\) is the number of times that event \(j\) was observed. The likelihood function is a measure of the possibility of a particular probability value, and the method of maximum likelihood was used to estimate that probability. Through trial-and-error procedures, the most successful probability functions for predicting the various BGs are defined as (25):

\[
Pr_{BG=0} = e^{-a \cdot \text{BG} / b}
\]
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\[ P_{BG=\{1,2\}} = e^{-\frac{R_{max}}{b}} - e^{-a \frac{R_{max}}{b}} \]  
(13)

\[ P_{BG=\{3,4\}} = 1 - e^{-\frac{R_{max}}{b}} \]  
(14)

where \( a \) is a dimensionless factor to separate BG = 0 from BG = \{1,2\}, \( b \) is a weighting factor that governs the transition from low to high BG having dimensions of length, and \( R_{max} \) is the maximum bubble radius for the dive profile as predicted by the model. Figure 1 demonstrates the properties of \( a \) where its value is varied 4-fold from 1.25 to 5. For example, the probabilities for the occurrence of BG = \{1,2\} at \( R_{max}/b = 0.5 \) are 7.1, 32.0, and 52.4% for \( a = 1.25, 2.5, \) and 5.0, respectively. Alternatively, the respective probabilities for the occurrences of BG = 0, \{1,2\}, and \{3,4\} at \( R_{max}/b = 0.5 \) are 28.7, 32.0, and 39.3% for \( a = 2.5 \). Note that in this instance the probabilities must sum to unity. Greater weight is given to \( BG = 0 \) for small \( a \), and as the value of \( a \) increases the crossover point between \( BG = 0 \) and \( BG = \{1,2\} \) moves toward lower values of \( R_{max}/b \) (also note that the curve for \( BG = \{3,4\} \) does not depend on the value of \( a \) as defined by Eq. 14). Finally, with increasing value of \( a \), the probability of \( BG = \{1,2\} \) exceeds that of the other 2 classifications over the intermediate range of \( R_{max} \) values. This flexibility coupled with the continuity feature of the probability spectrum represents an important improvement over the use of the binomial treatment in previous studies (4,5,7).

Since \( Pr \) is less than or equal to 1, the likelihood values become very small as the number of observations increase. It is prudent, therefore, to calculate the natural logarithm of the likelihood, denoted as the log-likelihood (LL) function:

\[ LL = m_1 \cdot \ln(Pr_1) + m_2 \cdot \ln(Pr_2) + m_3 \cdot \ln(Pr_3) \]  
(15)

Consequently, the LL values are negative and improvement through maximization is indicated with a decreasing amplitude in LL.

Substitutions of Eq. 12–14 into Eq. 15 leads to the following final form for LL for the trinomial bubble grouping:

\[ LL = \sum_{n=1}^{N} \left[ ND_0(n) \cdot \ln P_{BG=0} + ND_2(n) \cdot \ln P_{BG=\{1,2\}} + ND_4(n) \cdot \ln P_{BG=\{3,4\}} \right] \]  
(16)

where \( n \) is the dive profile number, \( N \) is the total number of profiles, \( ND_0(n) \) is the number of divers with a maximum BG of 0 for dive profile \( n \), and similarly, \( ND_2(n) \) and \( ND_4(n) \) are the number of divers for profile \( n \) that had a maximum BG of 1 or 2 and 3 or 4, respectively.

The LL value is dimensionless and only has meaning when comparing the value obtained between one model with that of another using the same interpretation of the data. Limits on the possible values of LL are defined by the following models:

Null model: Probabilities of the BG groupings are set to the observed proportions for that grouping over the entire data set. That is, \( P_{BG=0} = 0.425 \), \( P_{BG=\{1,2\}} = 0.281 \), and \( P_{BG=\{3,4\}} = 0.294 \) are fixed for each dive, thus ignoring the dive profile history and treating every profile exactly the same without any distinction in time, depth, or gas composition. This model was used to establish the minimum LL value that must be surpassed for significant parameter estimation.

Upper limit model: Probabilities of BG groupings were based on the actual occurrences for individual profiles without any distinctions made between the divers. For example, if
two divers in five had a BG outcome of 0, then the profile probability of obtaining BG = 0 is 0.4 and the first summation term in Eq. 16 would be 2 \cdot \ln(0.4). This model also circumvented the details of the dive profile history, but in this case the highest possible LL value from matching \( P \) values to profile outcomes for the entire data set was attained.

The likelihood ratio test (27) was used to determine whether an observed outcome was better predicted for a given set of trial parameter values \( S' \) against a previously established set \( S \), using the ratio \( \text{LL}(S')/\text{LL}(S) \). The logarithmic version of this ratio is the difference in the LL values and is termed the ratio statistic (D), i.e.:

\[
D = 2 \cdot [\text{LL}(S') - \text{LL}(S)]
\]

The ratio statistic was used to test whether improvements in fit were significant as additional parameters were considered. With each additional parameter, significant improvement (at the 0.05 level) occurs with respective increases in LL of 1.9, 3.0, 3.9, etc. units. All parameter values are given with the standard error of the estimate (±SE).

RESULTS

The best LL and corresponding parameter values for various parameter combinations are listed in Table 3. All models shown involve only one compartment since the addition of a second compartment did not result in any significant improvement. The parameters \( \tau_k \), \( k_{N_2} \), and \( b \) were estimated for all models and will be referred to as the standard set. The model names are coded to indicate the additional parameters that were estimated. The first portion of the code is a number followed by P to indicate the number of estimated parameters. This is followed by codes to identify these additional parameters: S for the tissue solubilities of nitrogen and of the solubility ratio helium/nitrogen, K for the helium rate constant expressed as a ratio against nitrogen, A for the probability parameter \( a \), G for the bubble surface tension, and V for the tissue volume. For example, model 7PSKA is a 7 parameter model with \( L_{N_2}, L_{N_2}/L_{N_2}, k_{N_2}/k_{N_2}, \) and \( a \) estimated in addition to the three standard parameters. The helium time constant was calculated from the tissue solubility estimates of nitrogen and helium, and from the estimated time constant of nitrogen using Eq. 10. When not estimated, the compartment gas solubilities and surface tension were based on human blood plasma (28), the probability parameter \( a \) was set to 3, and the tissue volume was fixed at 0.0001 cm\(^3\) (16).

Model 4PK estimated the nitrogen time constant, probability parameter \( b \), and linear rate
Model 4PK estimated the nitrogen time constant, probability parameter $b$, and linear rate constants $k^i$ for $N_2$ and for He (as a ratio against nitrogen), and was found to be a significant improvement over the Null model. The estimated nitrogen time constant of 67 min leads to moderately slow saturation of both inert gases in the tissue. However, the estimated ratio of approximately 2,000 unrealistically implies that the He is transferred across the bubble boundary by at least 3 orders of magnitude more rapidly than $N_2$. Such anomalies can arise due to the restrictive conditions placed on the limited number of estimated parameters based on the assignment of the other fixed parameters.

A further significant improvement was attained when the probability parameter $a$ was also estimated (5PKA). Its value became 2.55 and changes to the other parameters included a decrease in $\tau_{N_2}$ to 36 min, a small increase in $k^i_{N_2}$, and a reduction by half in $k^i_{N_2}/k^i_{N_2}$. The best 6-parameter model (6PSK) was the 4-parameter model with the two inert gas solubilities estimated. However, the solubilities predicted were considerably larger than the initial values based on blood plasma and higher by over an order of magnitude than that found in olive oil ($L^\text{sol}_{N_2} = 0.073$, $L^\text{sol}_{He} = 0.0168$ (18)) which is typically used to represent fatty tissue.

The best 7P model (7PSKA) combined features of the 5P and 6P models, that is, by adding the solubilities and the probability parameter $a$. The parameter values for the 7P model are all within the SE of their values for the 6P model, except for the additional parameter $a$ which changed to 2.55 (as it did in the 5P model). The added benefit of estimating parameter $a$ was a gain of about 10 LL units, which is comparable to the improvement found between the 4P and 5P models. Similarly, there was an improvement of about 30 LL units in both cases where the tissue solubilities were added (4P to 6P and 5P to 7P). Attempting to add either surface tension ($\gamma$) or tissue volume ($V$) as the 8th parameter to the best 7P model did not significantly improve the fit.

The best 9P model (9PSKAVG) was successful in significant LL improvement and realistic parameter estimations. The estimated Ostwald gas solubilities were $L^\text{sol}_{N_2} = 0.0438$
and $L_{ub} = 0.0096$, which are in the acceptable biological range, and the surface tension was estimated to be 5.0 dyne · cm⁻¹. Models with greater than 9 parameters were tested, but none led to any further significant improvement.

Figure 2 demonstrates the predicted bubble evolution for one of the standard air dives in the calibration data set using the parameters of the best overall model (9PSKAVG). In this case, bubble formation was predicted to occur soon after the start of decompression. Maximum bubble size is attained several minutes after surfacing and the subsequent rate of bubble dissolution proceeds less quickly than the bubble’s initial rate of growth. Also plotted in Fig. 2 are BG data observed from the six dive subjects who participated in this particular dive profile. For example, diver 1 had BGs of 3, 4, 4, 3, and 2 at approximately 110, 150, 200, 280, and 360 min, respectively.

The best overall model was tested on the additional dive dataset to determine how well it predicted the maximum bubble size and the probabilities for the different BG groupings. These predictions were based on the maximum calculated bubble size (Fig. 1) and the results are shown in Table 4. For the standard air dives to 45 msw for 30 min (29), the model underpredicted BG considerably because the majority of divers were observed to have high BG. All subjects participated in an experimental dive series to investigate the effect of exercise during decompression (30). These included trials where subjects were sedentary both at depth and during decompression. Subjects in these trials wore dry suits while sitting half-immersed in cold water; consequently, cold stress, which is presently not considered in the model, may have been a factor in the underprediction of BG.

The predictions were better for heliox divers on the 45 msw for 30 min dive, although the higher BGs were still underpredicted. These were working divers wearing dry suits in cold water. They breathed from a semiclosed circuit breathing apparatus (SCCBA) which supplied heliox based on a time-weighted average partial pressure of oxygen of 1.0 atm abs. Oxygen decompression was applied at 9 msw. The results (Table 4) are similar for the dry subjects on the SCCBA profile but breathing air instead of He (also with O₂ decompression at 9 msw) and performing light activity while supervising and tending the immersed working heliox divers.

The best predictions were obtained for the shallow air saturation dive (15 msw for 4 days). Decompression followed USN treatment table 7 (31) for which no bubbles were predicted to form, in concurrence with the observation.

**DISCUSSION**

The Upper Limit model had an LL value of −1,548 which is 650 LL units higher than that found for the Null model. That all the models fell within the quarter closest to the Null model indicates that there is considerable scope for improvement. The greatest gains in the prediction of BG occurred with 1) introduction of inert gas differences in gas transfer across the bubble boundary (40 LL units), 2) estimation of the inert gases’ tissue solubilities (23 LL units), and 3) estimation of the probability parameter $a$ (10 LL units).

Ideally, predictions should be made for each BG separately; however, there were insufficient data for that purpose as determined during preliminary estimation trials. The trinomial grouping contains two crossover points (Fig. 1); the first between BG = 0 and {1,2} represents the change from no bubbles to low bubble activity, and the second between BG = {1,2} and {3,4} represents the transition from low to high bubble activity. The probability functions used for the trinomial grouping (Eqs. 12–14) were chosen for their flexibility. Parameter $b$ provides a turnover radius for the large bubble grades, whereas parameter $a$ determines the split between no bubbles and some bubbles detected. Parameter $a$ can vary the maximum probability of the intermediate BG group through a
FIG. 2—Example of a standard air dive profile and the predicted nitrogen tissue tension and bubble evolution using the best overall model (9PSKAVG). Temporal distribution of recorded BG is shown in the shaded region for the six experimental divers where the diver identification numbers (1–6) are used to place their BGs using the "pressure" axis where 0 pertains to BG = 0 and 4 pertains to BG = 4.

Table 4: Predicted Maximum Bubble Sizes and Probabilities for Additional Profiles

<table>
<thead>
<tr>
<th>Dive Profile</th>
<th>Predicted Maximum Bubble Radius, cm</th>
<th>Predicted Probability of Bubble Grades: Observed Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 msw/30 min 32 divers (air)</td>
<td>0.0061</td>
<td>0, 1.2, 3.4</td>
</tr>
<tr>
<td>45 msw/30 min 18 divers (variable helix on SCCBA)</td>
<td>0.0054</td>
<td>37:22, 31:28, 32:50</td>
</tr>
<tr>
<td>45 msw/30 min 6 divers (SCCBA profile on air)</td>
<td>0.0052</td>
<td>39:17, 30:33, 31:50</td>
</tr>
<tr>
<td>15 msw/4 days 3 divers (air)</td>
<td>0</td>
<td>100:100, 0:0, 0:0</td>
</tr>
</tbody>
</table>

*Divers on air for entire dive (29).  *Customized helix profile for SCCBA with oxygen decompression at 9 msw (unpublished).  *Same profile as SCCBA, but divers breathing air with O₂ decompression at 9 msw.  *Air saturation dive with decompression according to USN treatment table 7 (31).  *Value is averaged because of the variation in O₂ pressure among divers.

A wide range, as demonstrated in Fig. 1, but seems to be narrowly fixed by the data set since all trials in which it was estimated returned a value ranging from 2.46 to 2.64. Consequently, all BG groupings have similar estimated probabilities in the neighborhood of $R_{\text{He}/b} = 0.4$.

Recall that in the 4PK model, the estimated $k_{\text{He}}:k_{\text{N₂}}$ ratio of almost 2,000 implied that He transfers across the bubble boundary much more rapidly than does N₂, thus allowing for quick growth and dissolution of bubbles when helium was added to or removed from...
the breathing mixture. That this ratio dropped by over an order of magnitude when the tissue solubilities were independently estimated indicates that inert gas differentiation is an important aspect of the bubble model.

At no point did a two compartment model outperform a single compartment model with a similar number of estimated parameters. This can be partially explained by the uniformity of exposure conditions in the data set (all dives were from short to moderate depths) despite the diversity in the types of dives conducted. A 2-compartment model would probably make a significant improvement with data of more varied exposure conditions since dives of greater depth and duration would probably require different kinetics from those estimated for the present data set.

The skewness about the estimated time constants for models 6PSK and 7PSKA (Table 3) was caused by a discontinuity in LL due to a single dive profile. This was an air dive to 27 msw for 22 min with O\textsubscript{2} decompression. Three divers were involved having maximum BGs of 0, 0, and 1. Predicting no bubble to form improved the likelihood for the first two divers but made the third diver’s outcome highly improbable. Thus, this one incident restricted the estimated \( \tau_{\text{kg}} \) to a value of less than 27.92 min since further increases in \( \tau_{\text{kg}} \) did not improve the fit for the rest of the dives by a comparable amount.

The best model estimates of the time constant (27.9 min) and tissue solubility (0.0438) of nitrogen convert to a blood perfusion rate of about 10 ml \( \cdot \) 100 ml\(^{-1}\) tissue \( \cdot \) min\(^{-1}\) which is 2.5 times larger than that estimated in a previous study (16). The estimated surface tension (5.0 dyne \( \cdot \) cm\(^{-1}\)) is rather low but consistent with that estimated elsewhere (32) for in vivo bubble formation. Such low values may reflect bubble formation in surfactant-rich environments or lipid micelle-like substances. Indeed, the estimated solubility of nitrogen (0.0438) suggests a tissue with a significant fat composition. However, this is contrasted by the estimated solubility of He (0.0096) which suggests a highly lean tissue type. This incompatibility cannot be resolved through kinetic considerations alone since the different gases’ rates of transfer into and out of the bubble were also independently estimated. Improvement in modeling in vivo bubble formation and growth requires further attention in both the transfer of gas between blood and tissue and between tissue and blood.

Bubbles were generally predicted to last up to 5 h after surfacing and had their maximum size occur within 2 h of surfacing (in general, the less stressful the dive, the earlier the maximum bubble radius was reached). Both of these features were found as a general trend in the BG observed in the divers in the present data set and as demonstrated in Fig. 2. The similarity in shape between the observed BG distribution and the predicted evolution of bubble size suggests that the model simulates in vivo bubble evolution reasonably well even though the BG temporal distribution was not part of the calibration algorithm. Only the maximum observed BG was used for calibration. This similarity also suggests that the BG history might be correlated to the evolution of bubble size, which will require further investigation of other profiles and observed BG.

For surface decompression dives, the surface interval (< 5 min) before decompression to 12 msw exhibits a temporary increase in the predicted bubble radius by usually not more than 20% over the size at the start of the interval (analogous to the increase in \( R \) seen in Fig. 2 during the final decompression step to surface). This prediction concurs with the finding that short surface intervals before recompression do not greatly increase the risk to the divers (17,33). Some consideration, therefore, might be given to redefining dive severity on the basis of an integrated bubble size (i.e., radius or volume). This is suggested by the general trend toward larger predicted integrated radii for profiles that have displayed larger proportions of high BG. Indeed, integrating BG over time has been
previously used to estimate relative dive severity (11). This trend does not fit every profile, but it does so with sufficient numbers to warrant its consideration in future analysis.

In conclusion, the bubble evolution model successfully predicted the outcome of dive profiles under similar conditions to that used in the calibration. The model clearly distinguishes outcome ranging from "no bubble" to "numerous bubble" events. The model that best estimated the BG outcome in the data set was one that incorporated a time constant for \( N_2 \), gas transfer rate constants for both \( N_2 \) and He, tissue solubilities for both inert gases, probability parameters \( a \) and \( b \), surface tension, and tissue volume. The estimated parameters were all within the range of human biological values despite some incompatibility between the estimated tissue solubilities of He and \( N_2 \).

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