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FUNDAMENTAL BIOPHYSICAL ASPECTS OF DECOMPRESSION SICKNESS

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INTRODUCTION

The work described in this report is directed at determining the physiological and physical factors which underly the formulation of safe decompression procedures. Some aspects are continuations of studies initiated by the principal investigator at Duke University under contract N00014-67-A-0251-0015. Almost all of the work has been published or is currently in press and a full list of publications arising from these contracts is appended to this report. This report summarizes the results and then goes on to describe the way in which the principal investigator now envisages decompression sickness and its prevention in the light of these and other published studies.

OBJECTIVES

To elucidate the mechanisms of several categories of decompression sickness with particular emphasis upon the basic physiology and physics which underly the formulation of methods for prevention and treatment. These are not necessarily the most interesting topics to follow academically but are issues which need to be resolved in prescribing decompression from fundamentals. The emphasis is one of "looking into" the body to see what the bubbles are actually doing in the living tissues rather than the more common approach of using the occurrence or non-occurrence of decompression sickness as the sole criterion for evaluating the procedure.

Specific categories of decompression sickness which have been studied in this way include limb bends, air embolism and vestibular DCS. Particular attention has been paid to factors which might potentiate neurologic symptoms and whether it is really feasible to invoke calculation as a means of avoiding Type II decompression sickness. In view of the influence of pulmonary oxygen poisoning, methods for predicting its onset and detecting it by direct monitoring of the subject have been included in this study.

Specific questions

The specific questions for which answers were sought included the following.

1. Are limb bends mediated ischemically or do they have a simple mechanical basis?

2. Since it is difficult to invoke more than one anatomical tissue in the aetiology of decompression sickness, what is its anatomical identity?

3. If the tissue responsible for limb bends is tendon or a similar "tight" connective tissue, what is the nature of the circulation within it and how would it eliminate inert gas during decompression?

4. When would bubbles form and how do they behave in such a tissue?

5. Is there a better animal model than the goat in which to study limb bends as opposed to other forms of decompression sickness which are not the presenting symptoms in man that limb pain is?

6. Can cerebral and, possibly, other neurologic categories of decompression sickness be induced by impairing the ability of the lung to filter the many venous bubbles which are otherwise "silent" during decompression?

7. What factors can compromise the capability of the lungs to trap microbubbles?

8. How can we produce microbubbles extracorporeally and what is the threshold diameter for their filtration by the pulmonary circulation?

9. How can we detect microbubbles in the arterial system?

10. If we administer agents likely to impair the ability of the lung to filter microbubbles, does this increase mortality from decompression sickness?

11. What agents are likely to affect the ability of a pulmonary vessel to stop a bubble of greater diameter and is lung surfactant one of these?

12. How does surface tension vary with surface area under physiological conditions - as opposed to those often employed in surface balance studies?

13. Has the contact angle been overlooked in previous studies *in vitro* and does such a parameter also apply *in vivo*?

14. How does a contact angle influence the ability of a pulmonary vessel in stopping a bubble from passing into the arterial system?

15. Does alveolar surfactant migrate to the venous emboli trapped in the lung and does this pose a danger to delayed recompression of a diver?

RESULTS AND DISCUSSION

These are, perhaps, best described according to the questions listed above:

Kangaroo rat as a model for limb bends

It is highly desirable to have a small animal model for limb bends as opposed to the death-or-recovery criterion used on other small rodents, since

local limb pain ("the bends") is the presenting symptom in 85-95% of cases of decompression sickness in divers and compressed-air workers. We have undertaken an extensive survey of tail-biting in the kangaroo rat as a much more convenient alterative to hoof-lifting in the goat as a means of testing diving tables.

This study (1) involved 720 exposures of 70 kangaroo rats trapped in West Texas and showed that decompression-induced tail biting in this animal provides a good animal model for marginal limb bends in man. That this phenomenon can be reversed by recompression and pathological examination of the tail both indicated that a similar mechanism is probably involved in kangaroo rats and humans. Quantitatively, the most susceptible 20% of kangaroo rats can reproduce the no-stop decompression limits for man for exposure times ranging from 5 min to 8 h, for both air and helium-oxygen. Even the average minimum no-tail-biting depth of 46.2 fsw (2.40 ATA) for this species is much closer to the minimum bends depth of man than to the equivalent depth for other animals of its size, and is as good as the goats'. Its size and habits make the kangaroo rat much more convenient than other animals to use as a model for marginal decompression sickness, and particularly attractive economically for testing long helium-oxygen schedules and other means of decompression sickness prevention.

Anatomical identity of tissue

In the above study (1) it was particularly significant that bubbles were found between the tendon fibres of the long tail in the locations where the decompressed animal had been biting before it was sacrificed. It tends to confirm much other evidence which the prinicpal investigator has collected from many other studies (2) to implicate tendon or a similar "tight" connective tissue as responsible for limb bends.

Ischemic vs. mechanical basis for limb bends

There is a certain reluctance to attribute different mechanisms to different categories of decompression sickness and the old concept of "nitrogen bubbles in the blood" is often offered as the explanation for all undesirable manifestations of inadequate decompression. However, in its most common form, viz. limb bends, intravascular bubbles would need to induce pain ischemically whereas the extravascular bubble would do so mechanically. This fundamental difference has been exploited in the following study (3) designed to differentiate between these mechanisms.

We used 20 kangaroo rats to investigate the effect of exposure to low oxygen levels (0.11 Atm O_2 inspired partial pressure) prior to decompression from a steady-state condition. This hypoxia was found to afford significant protection against limb bends as simulated in those animals by tail biting. Yet, it potentiated neurologic symptoms compared with a control exposure on air with the same level of nitrogen supersaturation. However the incidence of simulated limb bends in the same animals was the same with hypoxia as with another control exposure at a pressure estimated to give extravascular

bubbles of the same size upon decompression. The results are, therefore, consistent with a simple mechanical basis for limb bends, but are difficult to explain by any ischemic mechanism since a general hypoxia exacerebates any pain produced by oxygen deficiency in the tissues. However, the reverse may be true for some forms of neurologic decompression sickness and the two such cases reported here are consistent with that view, although not statistically significant.

Gas transfer in tendon

Information on the dynamics of the vascular bed in living tendon seemed to be non-existant; although there had been a few studies (51) of vascular morphology in sacrificed animals. Hence it was decided that, if tendon really is the tissue responsible for limb bends, then it would seem wise to learn a little more about its circulation before getting too deeply involved in the perfusion vs. diffusion controversy. This is the issue which it was originally proposed to study concerning whether diffusion or blood perfusion limits the uptake and elimination of inert gases from tissues relevant to decompression sickness. However the observation (4) of a bundle phenomenon made this issue look somewhat less relevant than originally envisaged and led us to pursue our finding of intermittent flow in tendon following study as a much more rewarding avenue of research.

The capillary bed has been observed in the Achilles tendon of 40 bullfrogs and 10 guinea pigs for periods of up to 2 h. The opening and closing of adjacent capillaries in a perfused area follows the pattern originally described by Krogh for skeletal muscle but the frequency is slower, as anticipated from the lower metabolic rate of tendon; however, superimposed on this "flickering" is a much slower process whereby whole bundles of 20-147 capillaries open and close with little overlap in the tissue areas perfused by each. Periods of no flow averaged 39 min in 70 bundles followed in bullfrogs and 43 min in 34 bundles followed in guinea pigs, although a few failed to open in 100 min. This bundle phenomenon is discussed in relation to the serious implications in mathematically modeling the exchange of gases and nutrients between blood and tissue and the possible errors in assuming time averaging when determining blood perfusion rates. Also mentioned are the likely effects of decompression on closed bundles and the notion is introduced that the bundle phenomenon may be a factor determining which tissues can be injured by decompression.

Inert gas washout studies

The above findings were most surprising and certainly offered an explanation for the bursts of inert gas elimination found after 1-2 hours of washout - both from our study (5) and those of Barnard (52) and Vorosmartic et al. (53). Ours (5) differed from previous washout studies in so far as we kept to normoxic conditions at all times in an attempt to keep the physiological state of the subject the same and minimize any vaso-active effects of oxygen.

The elimination of nitrogen from each of 10 unanesthetized guinea pigs has been monitored after switching to a nitrogen-free breathing mix (normoxic $He:O_2$), either without decompression or on decompression to 2.21 or 1 ATA, following an exposure of 2 h at 4 ATA on normoxic $N_2:O_2$. Normoxic conditions were maintained throughout to avoid vasomotor effects of oxygen that could have complicated interpretations derived from previous studies. Results confirmed that inert gas washout rates decrease with decompression per se. This can be explained simply on the basis of the decrease in driving force for nitrogen elimination caused by depositing gas into bubbles where they form in tissue in a somewhat random manner. A very rough estimate shows that about 83% of all body tissue retained its gas in supersaturated solution on decompression to 2.21 ATA but only 79% did so at 1 ATA.

Bubbles produced in tendon

Bubbles produced in the Achilles tendon of guinea pigs by decompression have been observed in the living state under a high-powered microscope using an implanted optic fibre as a light source. Bubbles are seen to grow in non-perfused zones and to shrink in perfused zones. Thus the prinicpal investigator has proposed a concept (6) of alternating bubbles in formulating preventive decompression. The vital question which these studies leaves open is whether the capillary bundles open and close randomly or in sequence since a missed opening could enable a bubble to grow much larger than otherwise and so precipitate a bend however well that diving table was formulated.

This study also raises a serious question concerning the hitherto universal assumption that the uptake and elimination of gases are continuous processes. It also confirms the view originally expressed by the principal investigator (54) that conventional diving tables are really treatment tables rather than a means of preventing bubble formation.

Microbubble production and detection

The technique has been developed for producing microbubbles in a physiologically compatible infusion medium down to a diameter of 8 μm. This is a modification of the technique already described by the principal investigator (7) for making and sizing small bubbles. The difference is that the gas mix is 90-98% CO_2 and is injected into a physiological medium containing an isotonic concentration of Tris-buffer. This dissolves the CO_2, reducing the bubble diameter to as little as 8 μm or even less - i.e. to the size of red cells. The same techniques (7) can be employed to determine bubble size and size distribution, viz. the Coulter counter and an absolute method based upon terminal rise velocity.

The lung as a bubble filter

A new ultrasonic Doppler device has been used non-invasively over the femoral artery of anesthetized dogs to prove that it can detect carefully calibrated microbubbles of 14-189 μm diameter when these are infused directly into the aorta. The same evaluated technique has then been employed to detect

any bubbles escaping into the arterial system when gas was infused into the venous system either as microbubbles or as a bolus. Results from 18 dogs showed that, under normal conditions, the lungs are a superb filter for bubbles and that any cut-off diameter is less than 22 μm. However, bubbles escaped entrapment when the lungs were severely overloaded with gas (20 ml) or were pre-treated with a pulmonary vasodilator (aminophylline). The dog preparation and arterial Doppler device appear ideal for future studies to determine what other factors might compromise the capability of the lungs to filter microbubbles. Physiological parameters showed dramatic changes when bubbles were detected as escaping into the arterial system by comparison with their effect when retained within the lungs. It is our opinion, in the light of this work (8), that the lungs play a major role in determining whether the mass of silent venous bubbles formed by decompression escape into the arterial system and produce neurologic symptoms.

What factors compromise lung filtering capabilities?

Preliminary studies (9) indicate that several pathologic conditions can compromise the capability of the lung to trap venous microbubbles in the dog:

1. Hypovolemia (30-40% total blood loss)
2. Chronic O_2 poisoning
3. Overload which microbubbles (pulmonary vascular congestion)
4. Elevated CO_2
5. Excessive recompression

These findings raise difficult clinical questions concerning the excessive use of oxygen in treating decompression sickness and whether such a treatment as an 'overkill' for a limb bend could potentiate a neurologic 'hit'. Further tests of oxygen exposure (20 hours at 1.5 Atm O_2) seem to confirm this suspicion, although there seems to be great variability in the degree to which the same oxygen exposure can compromise the filtering capability of dog lungs. There is also the possibility that emboli other than bubbles will also escape entrapment.

Many more trials are needed before recommendations could be made regarding recompression but, if substantiated, our preliminary results would support the concept of not recompressing a limb bend beyond the depth of relief for fear of releasing trapped venous bubbles and precipitating a neurologic case.

Pulmonary vasodilators

An experiment has been devised to test the above theory that the state of a subject's lungs and, in particular, their capability for trapping venous air emboli, can determine whether a particular decompression will lead to a state of wellbeing or to serious neurologic injury. This study involved 193 rats exposed to 6.8 ATA for 130 mins on air. When aminophylline (0.15 mg/g) was administered post-decompression, mortality increased from 50% to 71%, the increase exceeding the 99% level of statistical significane. Aminophylline

was chosen as a potent pulmonary vasodilator known to compromise the capability of the lung to filter out venous microbubbles. Hence the increased mortality induced by this agent is attributed to the impairment of normal bubble trapping - a capability upon which the body is evidently dependent in preventing the many "silent" venous bubbles normally produced by decompression from escaping into the arterial system and causing serious neurologic problems.

Oxygen tolerance

Indices of oxygen poisoning in the lung are of two types - predictive and subjective. Predictive indices invoke calculation to estimate what degree of insult will be imposed upon the lung by a particular exposure. Hence we developed the Cumulative Oxygen Toxicity Index (COTi) as an alternative (11) to the UPTD since the latter cannot allow for regression of the injury upon returning the subject to a sub-toxic breathing mixture.

Subjective indices are really to be preferred where the subject is continually monitored during the exposure. Vital capacity has not proven reliable and, in any case, its measurement depends upon a conscious effort by the diver. We have developed an alternative (11) which correlates well with pathologic findings and would be easy to adapt to a decompression chamber.

In this study (11), the ratio of mid-inspiratory to mid-expiratory flow ($\dot{V}_I/\dot{V}_E$) has been measured on rabbits subjected to various hyperbaric oxygen exposures. In previous studies of chemical insults to the lung, this index has been shown to offer a good correlation with reduction in compliance, increased oedema and histopathological findings; while gross pathologic examination has confirmed the same tendency with oxygen. The ($\dot{V}_I/\dot{V}_E$) ratio therefore appears to be a very convenient index of pulmonary O_2 toxicity and has the great advantage that it is independent of breathing frequency and can be applied with no conscious maneuver required on the part of the diver, patient or experimental animal.

In normal rabbits the average value of this index is 0.88 and varies no more than 0.08. The index starts rising when the oxygen exposure exceeds 0.5 Atm and at 1.5 Atm, for example, reaches a value of 1.55±0.05 after 21 hrs. Death has occurred when the index reached 2.5. Upon return to normoxic conditions, the index immediately starts to decrease and continues to do so for another 3-4 hrs. After that, however, the index rises and reaches a peak value 30-50 hrs following return to normoxic conditions. The peak value is variable but often far exceeds the rise initially induced by oxygen breathing. This has serious implications concerning repetitive dives following high oxygen exposures.

Mechanism of bubble release in lungs

The prinicpal investigator (2) has pointed out that, in their eagerness to locate at fluid-air interfaces, surfactant molecules would be as likely to be deposited at the surface of bubbles trapped in pulmonary microvessels

as they are at the alveolar lining where they are known to be found. Our current work involving back-flushing of embolised lungs shows definite evidence of surfactant migration.

This is particularly interesting since it offers surfactant migration as a slow process explaining the long delays often recorded in the appearance of arterial bubbles from an embolised lung (30-60 mins). It also raises further quesions concerning excessive recompression as a treatment. Recompression would reduce surface area and, hence, surface and surface tension allowing even pulmonary arterial pressure to push a bubble over to the pulmonary vein. This has led to several basic studies of lung surfactant of which dipalmitoyl lecithin (DPL) is known to be the most surface active. These include:

1. An assessment (12) of the instrument conventionally used in pulmonary studies to measure surface tension. The surface properties of over 250 films of dipalmitoyl lecithin (DPL) and Tween 20 on distilled water have been investigated using two different surface balances simultaneously - the Wilhelmy balance, popular in physiological studies, and the Du Nouy ring method whose readings are independent of contact angle. Using concentrations of DPL ranging from 0.08-1.90 μg cm^{-2} on a Langmuir trough where the pool area was cycled from 100 to 27.5% of maximum, the Wilhelmy balance registered virtually the same force per wetted perimeter as the ring method for both pure water and Tween 20, but appreciably lower values for DPL over the whole cycle. The above differences can be explained on the basis of a significant (45°-70°) contact angle - a surface property also demonstrated photographically and by direct measurement. Contact angle was shown to vary with pool area - a relationship exhibiting hysteresis. This study indicates that the Wilhelmy balance has been an unfortunate choice of instrument for studying DPL films whose surface tensions are appreciably higher than previously estimated.

2. Surface tension under physiological conditions (14). The surface tension of 161 films of DPL have been measured on a Langmuir trough using a Wilhelmy balance conditions controlled to stimulate the state of the alveolar lining *in vivo*. The paramenters controlled were temperature (maintained at 37°C), humidity (100% at 37°C), surfactant concentrations (encompassing the best available estimates), area changes (consistent with normal respiration), frequency adaptation to continuous cycling and composition and pH of the aqueous hypophase. Simultaneously maintaining all of these parameters within the best estimates of physiological limits, the relationships between surface tension and surface area showed appreciable differences from previous studies, our results showing higher minimum values of surface tension, appreciably less change in surface tension with compression and far less hysteresis between surface tension and surface area. The higher minimum values are consistent with original estimates of alveolar surface tension made by von Neergaard - viz. 35-41 dyne cm^{-1}. The appreciably smaller change in surface tension with change in area is discussed as detracting from

the relevance of surfactant in imparting alveolar stability. The reversibility between surface tension and surface area under physioloigcal conditions is discussed in connection with compliance hysteresis which is considered to be more dependent upon geometric irreversibility of the alvelolar surface than upon any intrinsic property of the surfactant.

3. Relating findings to excised lungs (15). A method has been devised for measuring FRC in the intact sacrificed animal or absolute lung volumes in any excised lung preparation without changing the inflation pressure. This is achieved by titrating the absolute pressure of a chamber in which the preparation is compressed until a known volume of air has entered the lungs. This technique was used to estimate the volumes of five intact rabbit lungs and five rigid containers of known dimensions by means of a Boyle's Law relationship. Results were found to agree to within ±1% with values determined by alternative methods. In the discussion, the advantage of determining absoulte lung volumes at almost any stage in a study of lung mechanics without the determination itself changing inflation pressure and, hence, lung volume is emphasized.

4. Demonstrating (16) lung surfactants can induce a contact angle at biological surfaces. A contact angle (θ) has been measured at the surface of dog tracheal epithelium by means of two surface balances simultaneously monitoring the apparent surface tension of the same film in a Langmuir trough - one method dependent upon θ and the other independent of θ. This was confirmed by direct observation. The contact angle was absent for Ringer's solution alone but was induced by DPL deposited on the fluid surface in physiological concentrations. The contact angle varied from 0° to 67° for compression of the DPL film from 100% to 27.5% of its original area and displayed hysteresis with respect to area. These findings show that DPL has unusual surface properties in reducing surface tension yet decreasing wettability, i.e. acting as an anti-wetting agent. The physiological advantages of this unusual combination of properties are discussed in relation to maintaining pulmonary homeostasis and the forward propulsion of mucus which could be facilitated by the differential wettability of cilia induced by DPL. One possible disadvantage of DPL is indicated where fluid plugs might seal an airway - such as in the newborn.

The discovery of a contact angle *in vivo* has serious implications since it would impair the ability of a pulmonary vessel to retain a bubble, i.e. a lower pulmonary artery pressure would be needed to push a bubble through to the left heart. This, again, emphasizes the role of the lungs in determining the occurrence of some forms of neurologic decompression sickness - if not all forms.

Vestibular decompression sickness (17)

Gaseous supersaturation can be induced under steady-state conditions when two inert gases are transmitted in opposite directions across any

system comprising a diffusion barrier adjacent to a zone of limited convective capacity. This has many implications for bubble formation *in vivo* and can explain the occurrence of symptoms of decompression sickness without decompression.

This model would seem preferable to that based upon counterdiffusion since it does not involve a thick layer of lipid and can therefore explain isobaric vestibular symptoms since the inner ear is virtually fat-free.

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