ASPECTS OF NEUROLOGICAL DECOMPRESSION ILLNESS: A VIEW FROM BETHESDA

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Abstract

A minority of divers with neurological decompression illness (DCI) fail to improve with recompression treatment. This is particularly seen in cases where features of severe spinal cord injury develop soon after surfacing. Haemorrhage into the spinal cord is implicated in the pathogenesis of these cases and evidence is presented that supports the view that the bleeding coincides with shrinkage of autochthonous bubbles. The role of hyperbaric oxygen therapy in the treatment of spinal cord DCI is discussed with reference to possible benefit in ischaemia-reperfusion (I-R) injury. Similarities and differences between the tissue injury of dysbaric and conventional spinal cord injury are outlined. The implications of advances in drug therapy for conventional spinal cord trauma are considered in the context of their potential application to treat neurological DCI.

Introduction

Diving medicine retains enormous challenges, and exchange service with the United States Navy in the Naval Medical Research Institute (NMRI), Bethesda, Maryland, provides a Royal Naval medical officer with unique experience in military diving medicine that is no longer available in Britain. The following account briefly summarises the author’s personal view of several issues related to neurological decompression illness (DCI) and its treatment.

Most patients with DCI respond well to conventional recompression therapy, but treatment is ineffective for an important minority of cases. Clinically, these cases tend to have neurological features suggestive of spinal cord injury and are either cases with early onset of severe signs or cases where there is significant delay before initiating recompression therapy. There is no generally accepted explanation for these treatment failures.

The pathological mechanisms for dysbaric central nervous system (CNS) injury are complex and remain controversial. Where the condition is due to excess gas burden (as distinct from pulmonary barotrauma with gas emboli) several mechanisms may contribute to the disease process in varying degree, depending on the circumstances. Extra-vascular (autochthonous) bubbles are most likely in short latency cases, gaseous emboli, venous infarction, and ischaemia-reperfusion effects being predominant in cases with delayed onset. However, for many years it was assumed that the main problem was of ischaemia due to the persistence of inert gas bubble emboli in blood vessels. In refractory cases, this assumption led to therapeutic efforts to eliminate any causative bubbles as rapidly and completely as possible by recompression to greater pressures (depths), by lengthy saturation treatments, or by the breathing of exotic gas mixtures. Use of these measures has been largely empirical and, unfortunately, none of them has proved convincingly effective. Indeed, there has been little real advance in the treatment of DCI since the introduction of the short oxygen recompression tables (RN Tables 61 and 62) in the late 1960s and early 1970s. Difficulty in standardising the terminology used to describe the various presentations of DCI have frustrated efforts to set up appropriately randomised therapeutic trials.

The author’s work in NMRI has been to develop an animal model of neurological DCI with which to evaluate treatment strategies and identify modifiable risk factors for DCI. The animal used for the model is the pig, which has many anatomical and physiological similarities to humans.

The pigs undergo a simulated “dive” to a pressure equivalent to 200 feet of seawater (fsw) (61.2 msw) (612.6 kPa), for 24 minutes, in a dry compression chamber, breathing air. This pressure exposure produces a 70-75% incidence of neurological DCI. Pigs that develop the condition are given appropriate sedation and iv. fluids, and are treated by recompression and oxygen on RN Table 62 (USN Table 6) in a manner analogous to human divers. The time from diagnosis of DCI to commencing treatment is 10-20 minutes. The success of treatment is judged 24 hours later by assessing the pigs’ ability to run on a treadmill. Pigs are then anaesthetised, euthanised, and undergo a detailed pathological examination.

Haemorrhage and the pathogenesis of dysbaric spinal cord injury

In 1908, Blick reported one of the largest series of autopsies on divers with fatal DCI. When describing the gross appearance of the spinal cords from these cases, he wrote: “... it looks as if one has stippled the face of the section (of the spinal cord) with a fine knife or needle ... with this condition is nearly always associated haemorrhage of greater or less extent”. He goes on to recount: “... they (the haemorrhages) may range in size from mere points of blood to, as I have seen in nine cases, large haemorrhages practically cutting the cord in two”. Several other authors, notably Brooks in 1907, Smith, and Jaminet and Clarke in the 1870s, all describe acute haemorrhage in the cord or its membranes as a marked feature of DCI. Despite such descriptions, until recently the role of CNS haemorrhage in the neuropathology of DCI in divers received little emphasis in most diving medicine texts.
During our studies of neurological DCI in pigs, it was soon noted that those pigs with early onset of neurological signs were often little improved by recompression treatment. At necropsy, these refractory cases were associated with petechial haemorrhages, grossly visible in the spinal cord (Figure 1), which appeared remarkably similar to the historical descriptions of human cases. On histological examination of the spinal cords from these pigs, microscopic haemorrhages such as those illustrated in Figure 2 were a typical finding. Pigs that responded well to recompression treatment invariably had no or minimal haemorrhage in their CNS on histopathological examination.

Further information is available: We investigated the timing of the haemorrhage in an attempt to differentiate bleeding due to mechanical disruption of micro vessels from bleeding into areas of infarction. Blood was taken from each of 15 pigs and the erythrocytes were labelled with a fluorescent marker. The labelled red cells were then reinjected into the 15 pigs at different stages in the disease process; before diving in three; on DCI onset in three; immediately before recompression treatment in three; and 10 minutes after reaching treatment pressure (60 fsw) (18 msw) (183.8 kPa) in the remaining six pigs. On the day after diving, pigs were euthanised, perfusion fixed, and necropsy was performed. Frozen sections of spinal cord were made. Areas of haemorrhage were located by

![Figure 1. Spinal cord with petechial haemorrhages.](image1)

![Figure 2. Cross section of spinal cord with multiple white matter haemorrhages (x25 H & E).](image2)
microscopy of frozen sections stained with haematoxylin and eosin, then the same areas of haemorrhage in adjacent, unstained, frozen sections were examined by fluorescent microscopy for the presence of labelled erythrocytes. The concept was that fluorescent cells would be absent from haemorrhages that had formed before injection of the labelled erythrocytes, but fluorescence would be present if the haemorrhages took place while labelled erythrocytes were in the pig’s circulation.

Labelled red cells were found to be present in the haemorrhagic cord lesions of all nine pigs reinjected before recompression treatment, but were absent in the six pigs where the labelled cells were reinjected 10 minutes after recompression. This finding suggests that the haemorrhage coincided with recompression. A mechanism whereby autochthonous bubbles disrupt micro vessels, which then bleed when the bubbles shrink on recompression, would explain this finding. Such a mechanism can also explain why some human cases deteriorate rapidly during or soon after the start of recompression treatment. The sudden relapse seen in some cases after, or in the late stages of initially successful, recompression treatment can be explained by secondary haemorrhage. One can also speculate that, in the absence of recompression, bubbles will shrink naturally over time and in cases where micro vessels have been damaged, delayed bleeding may occur, perhaps into an area of infarction or ischaemia.

In retrospect, haemorrhagic lesions have been described in previous models of acute DCI in dogs and goats, and a photograph of petechial haemorrhage in the cord from a human victim of severe neurological DCI, who died six days post-dive, has recently been published. It seems likely that severe, short latency, human DCI shares a common pathology with the animal models; namely, the potential for acute haemorrhage into the spinal cord. However the clinical significance of this has not been clearly stated: cases where haemorrhage has occurred are likely to be resistant to standard treatment; recompression and oxygen will shrink bubbles and increase tissue oxygenation, but the consequences of haemorrhage into CNS tissue will not resolve acutely.

The above findings do not, of course, imply that we should avoid recompressing patients with early onset of neurological signs for fear of precipitating haemorrhage, but they have implications for both the management and prognosis of diving cases in certain circumstances. For instance, the understanding that CNS haemorrhage rather than just gas bubbles may contribute to the clinical condition of the patient, might alter a decision to compress a severely ill or deteriorating patient beyond the 18 msw (60 fsw) pressure of Table 62, and thereby commit them to a lengthy saturation decompression. The question that defines the clinical management rationale in such cases subtly shifts from, “Is recompression treatment good for eliminating bubbles?” for which the answer is “Yes” to the question, “Is hyperbaric oxygen good for treating nervous system dysfunction associated with haemorrhage?” to which the answer is “Possibly, but we don’t really know”.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) therapy, where the patient breathes oxygen in a pressurised chamber, is the main treatment modality for acute DCI. The initial beneficial effect of HBO is generally accepted: tissue oxygenation in general, and the oxygenation of injured or ischaemic tissue in particular, is improved due to simple diffusion. Arteriolar vasoconstriction lowers capillary pressure and limits oedema. Simple recompression shrinks bubbles, while the raised partial pressure of oxygen accelerates the elimination of inert gas by enhancing the diffusion gradient between tissues and blood. Animal studies suggest that physical gas bubbles are rapidly eliminated from CNS tissue, even in the absence of recompression. The injury that remains when the bubbles have gone results from the mechanical compression and distortion of CNS tissue that they caused, the damage to vascular endothelium, activation of inflammatory mechanisms and the consequences of micro-vascular stasis. Histologically, the acute injury typically manifests as disruption and oedema of axons, haemorrhage, ischaemia/infarction, or a combination of these (Figure 3). Repeated recompression treatments of DCI victims are carried out under the assumption that HBO is of benefit in these conditions. This is the accepted standard of care, but there have been no appropriately controlled studies to confirm the efficacy of repeat treatments. The difficulty is in distinguishing the clinical improvement that frequently occurs over time in untreated cases, from a therapeutic effect of HBO.

Despite the comments above, there is growing indirect evidence of mechanisms by which HBO could benefit the tissue injury in spinal cord DCI. Whatever the mechanism of injury, reversible microcirculatory stasis may occur and initiate a complex series of events resulting in the “no-reflow” phenomenon or ischaemia-reperfusion (I-R) injury. Our knowledge of the mechanisms of I-R injury derives from many areas of biomedical research, but evidence for clinical efficacy of HBO in this condition comes mainly from work in the context of reconstructive surgery. Leucocytes are known to adhere to damaged vascular endothelium at the site of I-R injury and promote cell damage by production of oxygen free-radicals, which induce lipid peroxidation. Lipid peroxidation is a process that spreads across cell membranes and disrupts the physiological ionic gradients across the membrane. It impairs the normal function of phospholipid-dependent enzymes and, if sufficiently severe, results in membrane lysis. In addition to oxygen radical production, adherent leucocytes are known to
release a number of vasoactive substances that induce spasm in local arterioles and contribute to post-injury hypoperfusion and ischaemia.

In skin flap models of I-R injury, HBO has repeatedly been shown to increase flap survival. This may be explained by the finding that HBO can dramatically reduce leucocyte adherence at the site of injury. A mechanism for this effect has been suggested by Thom who showed that HBO reversibly inhibits leucocyte B2 integrin function, which is involved in the persistent adherence of leucocytes to vascular endothelium. HBO has also been shown to inhibit carbon monoxide-mediated lipid peroxidation of rat brain tissue. If HBO produces similar beneficial effects in damaged spinal cord tissue, then any clinical efficacy in human dysbaric CNS injury could be explained.

An analogy of dysbaric injury with conventional spinal cord trauma

Where mechanisms like I-R injury and haemorrhage are involved in dysbaric spinal cord injury, comparison with the disease process of conventional spinal cord trauma is appropriate. At a cellular level, the final common path of injury is likely to be similar but, grossly, there are several obvious differences. Firstly, the diver’s injury is not usually complicated by the need to stabilise vertebral fractures and manage hypovolaemic shock and other features of major trauma of which spinal cord injury is but one, albeit important, aspect. Secondly, actual traumatic section of all or part of the cord is not usually a feature in dysbaric injury. Thirdly, the disease process in DCI is typically one of multiple, small, predominantly white matter, lesions at different levels in the cord, rather than the single large focus of injury common in spinal cord trauma cases. In divers, therefore, the injury is mainly axonal and the neurone cell body (which contains the biomolecular machinery for cellular repair) is largely spared. This contrasts with the injury in conventional spinal cord trauma, which often manifests as a central contusion with maximal damage to the grey matter in the centre of the cord and lesser injury to the surrounding white matter. For the theoretical reasons above, the prospects for clinical recovery would seem better for divers. Anecdotally, this prediction appears to be borne out in practice, although good, long term follow-up studies in divers are lacking.

Work studying conventional CNS trauma suggests remarkable functional redundancy, even in the spinal cord. Experiments in animals indicate that as few as four to six
percent of normally functioning axons in a motor tract can sustain normal motor function in the muscle they supply. Furthermore, these experiments suggest a threshold effect whereby an increase in axonal survival from less than three percent to more than six percent, in tracts passing through the site of injury, converts paralysed muscles to muscles with normal movement. The implication for recovery of both dysbaric and conventional spinal cord injury is that even a small improvement in physiologic axonal survival may produce dramatic clinical benefit.

Studies of HBO treatment in conventional spinal cord trauma have been inconclusive although controlled animal studies have suggested benefit. Interpretation of the human work is beset by problems of delay to treatment and the use of different partial pressures of oxygen.

**Future adjunctive drug therapies**

Turning to the prospects for improved therapy of dysbaric CNS injury, it is likely that these will arise from improved treatments for conventional spinal cord injury. This subject has recently been concisely reviewed by Hall and Braughler. Considerable progress has been made following the demonstration, in 1991, that high-dose methylprednisolone improved the outcome for human spinal trauma patients. The mechanism of action of the methylprednisolone is now thought to be due, not to an effect on glucocorticoid receptors or oedema, but to a reduction in oxygen radical-mediated lipid peroxidation of injured cell membranes and inhibition of post-injury hypoperfusion. The importance of commencing treatment within eight hours of injury was highlighted by the methylprednisolone study and the finding of this "therapeutic window" for drug treatment may have implications for the timing of HBO treatment of dysbaric spinal injury.

A variety of other pharmacological strategies which involve anti-oxidant drugs and/or inhibitors of lipid peroxidation show great promise as future therapy of CNS injury. Perhaps the most exciting potential therapeutic advance is the development of a non-glucocorticoid class of steroids, the 21-aminosteroids or "lazaroids", which are potent inhibitors of iron-catalysed lipid peroxidation. This is particularly interesting because both the formation of oxygen radicals and the process of lipid peroxidation in the CNS may be catalysed by iron and haemoglobin from extravasated erythrocytes at a site of haemorrhage is an obvious source. The efficacy of one lazaroid, tirilizad mesylate, has been demonstrated in vivo in controlled, blinded studies in animals. Currently, phase III human trials in head injury, subarachnoid haemorrhage and spinal cord trauma are in progress and the results are eagerly awaited. Their potential relevance to the management of dysbaric spinal cord injury is obvious.

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The experiments reported herein were conducted according to the principles set forth in the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council, DDH, Publ. No. (NIH) 85-23.

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**ASMA-UHMS DCS WORKSHOP THOROUGH AND WELL ATTENDED**

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As an example of inter-society collaboration on a topic of mutual interest, treatment of decompression illnesses, and in terms of gathering probably the best collection of experts on this subject that have ever been assembled, the Workshop was an outstanding success. In terms of achieving consensus of the experts on some key issues, success was somewhat more elusive. Since this workshop’s configuration and auspices were laid out in the lead article *Pressure* [24(3), May 1995] we will not repeat them here. Its official goals, what was wanted in the way of consensus, were perhaps not so well laid out (as opposed to objectives, the mechanism for reaching those goals). Organizers and chairmen were Paul Sheffield and Richard Moon.

Basically it was hoped that uniform treatment procedures could be agreed upon that would permit defining the requirements of treatment, hence its cost. This is important to DAN, who has to pay for treatments. It is reasonable to try to set limits to how many post-treatment recompressions might be needed, for example, but by all appearances this group was not ready to sign on for this.

Lest this imply that the meeting was anything but outstanding, please note that these participants had 2 days (including an evening session) of concentrated and well-prepared presentations by the world leaders in decompression and decompression illnesses. This included everything from reviews of NASA’s and DAN’s experience and experience of various navies, all the way to the devastating decompression sickness not being treated at all well on the Miskuito coast of Central America. The program included most of the heavy-weights, but sitting there on the front rows were many others not on the program but with plenty of experience to share. Being with this group for a couple of days was a real treat professionally.

To begin with we got a neurological and neuropathological orientation that started us off well. Drew Dutka’s chart of DCI made a lot of sense out of this slightly troublesome terminology. John Hardman’s pathology states that irreversible damage begins within 10 minutes. Next the “aerospace” portion that included altitude DCS and the effects of oxygen pre-breathing as well as some provocative possibilities (by Mike Powell) to explain why astronauts are so “resistant” to DCS. Pat Kimbrell presented a crisp and well thought out table for treatment of altitude DCS. Differences showed up on treatment with Table 5 after altitude DCS; USAF uses it with few recurrences, Canadian experience says it causes too many. In fact, it seems Table 5 split the group down the middle; it will be interesting to see how the balloting went on this one. Ed Thalmann reviewed the history of treatment table development, noting that the need for decompression following treatment was not immediately recognized. Table 5 works if the rules are followed. He sees no specific benefit from helium except in the ensuing decompression. Embolism as an entity was covered, a refreshing view since the advent of “DCI” has tended to subvert the use of that term, unfortunately. The advice from Des Gorman is to treat the mechanical effects (the bubble), then the damaging effects of bubbles. A lot of embolism cases resolve spontaneously, some never do.

If this Workshop made one decision, it was that early treatment is beneficial. This was a prevailing theme throughout, and no one had any arguments against it, even if the only chamber available is a monoplace chamber, a distinctly new consensus over some older viewpoints. Yehuda Melamed reviewed the successful Israeli experience with transportable chambers in the early 1970s. Gary Beyerstein mentioned that the more enlightened commercial companies no longer have penalties for being treated, a tactic that gets divers who need it in the chamber quicker; others can learn from this success. David Elliott acknowledged that commercial diving is boring these days, since there are so few hits. Once again, the concept of recompressing first and asking questions later is endorsed.

Another feeling that seemed present was that the treatment levels that have been used are at a marginally toxic level of oxygen. The treatment with 100% oxygen at 2.8 atm is a compromise to get the maximum compression at an oxygen level that can be tolerated; it works, but the O₂ level is higher than desirable and 2.5 atm may be better.