MECHANISMS OF SPINAL CORD INJURY IN DCI

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Abstract

After more than a century of research into the mechanisms of spinal cord injury in decompression illness (DCI), there are reasons to believe that neither of the two principal mechanisms which have been proposed apply in all instances. Arterial gas bubble emboli are probably rare in non-lethal presentations and should preferentially injure highly perfused organs because they receive most bubbles. On the basis of blood flow, one would expect the grey matter of the cord to be the principal target, whereas it is in the white matter that the lesions of DCI are normally found. Venous infarction is not only a very rare cause of spinal cord dysfunction but the histology of massive, central infarction differs from the scattered, punctate haemorrhages which are classically seen in DCI. An alternative mechanism, the formation of extravascular bubbles within the substance of the cord, so-called autochthonous bubbles, received little attention until the late 1980s.

An established canine model of severe DCI was adapted to study the acute histology of the disease and to compare it with that found after other insults. Numerous extravascular, non-staining, space-occupying lesions, located principally in white matter, were found soon after the onset of DCI. It is likely that they were caused by the local evolution of gas bubbles. These lesions were not present in undived controls, in dived animals which did not develop DCI or in spinal cords rendered dysfunctional by global ischemia or gas emboli.

Analysis of the size and distribution of these lesions in 5 cords indicated that they were sufficiently numerous to account for the loss of function. Recently, further doubt has been cast on the role of venous infarction, but the role of embolic bubbles remains controversial. It is concluded that no one mechanism can be responsible for spinal cord injury in DCI.

Key Words

Bubbles, decompression illness, hyperbaric research, physiology.

Introduction

Decompression illness (DCI) of the nervous system has been recognised since the early descriptions of the condition by Bauer[1] and Clark.[2] Involvement of the spinal cord was described as having an onset of a few minutes and sometimes a few hours after leaving the caisson or water. This is still a common presentation.[3] Patients presented with numbness, weakness or paralysis of the lower limbs, accompanied, on occasion, by a constricting girdle pain. Frequently there were disturbances of bladder, bowel and sexual function. The upper limbs, although occasionally involved, were usually spared.[4] Blick, who saw over 200 cases of "diver's palsy" among the pearl divers of Broome (60 of them post mortem) early this century, noted urinary retention was such a common consequence of diving that none of the divers would consider his outfit complete without a soft catheter![5] Bert observed that although neurological DCI may recover spontaneously, "Too frequently the paralyses of the lower limbs are persistent.... In none of the cases which we reported was a paraplegia which lasted more than two days ever completely cured."[6]

An aspect of neurological DCI that became apparent during World War II was the different distribution of symptoms in aviators compared with divers and caisson workers. In the latter group the spinal cord was, and is, more frequently involved than the brain and the onset may be without warning.[3,7-19] In aviators the central nervous system (CNS) involvement in DCI was mostly *cerebral* involvement, occasionally associated with "chokes" (cardio-pulmonary DCI) or cardiovascular collapse.[20-27] Spinal cord involvement was rare and usually transient[28-30] although occasional cases have been reported in man[12,31,32] and experimental animals.[33]

An intriguing aspect of this condition is that, despite considerable research efforts over the last century or more, the mechanism by which decompression injures the spinal cord remains far from clear. It is this issue that will be addressed in this presentation.

Spinal cord pathology in acute DCI

In 1870, Bauer described the post mortem examination of a 35 year old caisson worker who had survived for 5 days following the onset of acute neurological DCI.[1] The principal findings in the spinal cord were: hypervascularity of the dura and arachnoid mater, an accumulation of cerebrospinal fluid, the thrombosis of a moderately sized vein near the cauda and some softening of the cord. Spinal cord softening in this and other cases that he observed occurred in "circumscribed portions of the columns". Similar observations plus "small clots of extravasated blood on the external surface of the dura" were made by Clark[2] when commenting on cases which had died in a similar time frame.

Van Rensselaer published a review of 25 post mortem examinations of cases of caisson disease.[34]. The gross findings were essentially the same, with the additional observation of secondary tract degeneration in a man who had survived for 36 days. In this paper was one of the first descriptions of the microscopic findings in the spinal cord. He stated that the white rather than the grey matter was affected and, at the late stage of the disease represented by

these cases, the condition was characterised by the destruction of nerve tissue, increased neuroglia and the loss or atrophy of axis cylinders. He considered this to be degenerative or resemble a diffuse parenchymous "myelitis", with the lower dorsal cord most often affected. He found no evidence of haemorrhage. Sharples made similar observations on a tetraplegic diver who had died 38 days after the onset of DCI. There were scattered lesions throughout the cord, with the greatest tissue destruction at the cervical level.[35]

Many of the early reports of the neuropathology of DCI described cases in which death had occurred many days after the onset of the condition. Brooks described two cases in which death occurred after 3 days and 13 hours respectively.[36] In the first case he described an abundance of cerebrospinal fluid (CSF), patchy softening of the cord and a single, small, 'H' shaped haemorrhage at the level of T8. Microscopically, there was oedema and numerous "lacerations" in the firm parts of the cord and the softened areas presented the familiar appearance of "transverse myelitis". The spinal cord of the second case appeared considerably less softened and, although the spinal canal contained large amounts of blood, only tiny areas of haemorrhage were found within the spinal cord, principally located in the dorsal columns. Oedema, numerous "air lacerations" and microscopic haemorrhages were demonstrated histologically in the white matter of the cord.

Blick performed post mortems on 60 cases of DCI.[5] At the time of examination many had been dead for some time and had begun to putrefy. He also described the frequent finding of blood or blood-stained fluid in the dural canal. He described the cross sections of these cords as:

"It looks as if one had stippled the face of the section with a fine knife or needle, a semi-disintegrated appearance. With this condition is nearly always associated haemorrhage of greater or lesser extent".

Nine of his cases had large haemorrhages which were:

"Practically cutting the cord in two and filling the meningeal tube for over one and a half inches".

Although frequently quoted, this is the only description of such haemorrhages in the literature. Since the early 20th century the above pathological findings in the spinal cord have not been challenged although three additional features have been described. Kitano and Hayashi described a case in which spinal cord congestion was associated with the coagulation of blood in the epidural veins. These veins contained numerous fat droplets that were thought to be of bone marrow origin.[37] They also found, in a diver that had died from acute neurological DCI shortly after surfacing, several small (up to 1 mm diameter), non-staining, round spaces in the white matter of the brain and spinal cord.[38] Similar spaces were described by Waller in the brains of two scuba divers who had died underwater.[39]

Evidence of fat and bone marrow emboli has been found in animals, particularly in the lungs, but not in cerebral or spinal cord vessels.[40] Bubble-like lesions have been described in the spinal cords as well as other organs of dogs[41] and mice[42] suffering fatal decompression illness and in decompressed fingerling salmon.[43] In 1986 Palmer described a thin rim of sub-pial white matter, in the spinal cords of goats with DCI, that was invariably spared.[44]

The pathophysiology of DCI.

By 1891 there were almost as many theories of the mechanism of DCI as there were observers of the condition. Many of these hypotheses were based on scant evidence and conceived in the absence of a clear understanding of physics or physiology. They were fully reviewed by Van Rensselaer[34] who classified them as follows:

1 The theory of exhaustion and cold.
2 The gaseous theory.
3 The theory of congestion with sequelae:
   a "Black blood" (i.e. blood deprived of its oxygen.)
   b Evolution of gas in the blood vessels.
   c Haemorrhage.
   d Acute revulsive anaemia.
   e Comparative stasis.

He dismissed the first theory on the grounds that, in winter, many of the population are exposed to greater and more prolonged cold than caisson workers during their decompression, yet they do not display the signs of caisson disease.

The second theory has its origins in the observations of Robert Boyle[45] who decompressed numerous animals in his "exhausted receiver". One of Boyle's remarkable conclusions deserves quoting in full:

"Whether, and how far the destructive operation of our engin upon the included animal, might be imputed to this, that upon the withdrawing of the Air, besides the removal of what the Airs presences contributes to life, the little bubbles generated upon the absence of the air in the Bloud, juyces, and soft parts of the body, may by their vast number, and their conspiring distension, variously streighten in some places, and stretch in others, the vessels, especially the smaller ones, that convey the Bloud and Nourishment; and so by choaking up some passages, and vitiating the figure of others, disturb or hinder the due circulation of the Bloud? Not to mention the pains that such distensions may cause in some nerves, and membranous parts, which by irritating some of them in convulsions may

hasten the death of the animals, and destroy them sooner by occasion of that irritation, than they would be destroyed by the bare absence or loss of what air is necessary to supply them with."

Paul Bert,[6] in 1878, wrote, after a large series of experiments, mostly on dogs, that:

"Sudden decompression, beginning with several atmospheres, brings on symptoms of varying severity depending upon the degree of compression, the speed of decompression, the animal species, the individuals, and the state of the experimental animal at the time. These symptoms must be attributed to the escape of nitrogen which had been stored up in excess in the organism, following Dalton's law. This gas changes to a free state in the blood vessels, the different organic liquids, and even the interior of the tissues; it may therefore, according to circumstances, check the pulmonary circulation, soften and cause anaemia in certain regions of the nervous centres and especially the lumbar enlargement of the spinal cord, lacerate the tissues, and produce swellings or a more extensive emphysema. The severity of the symptoms depends upon both the seat and the extent of these multiple disorders."

Van Rensselaer criticised Bert's conclusions, saying that findings based on animal experiments, performed at higher pressures than those used in caissons, could not be extrapolated to man.[34] He adhered to the third theory. Although these various congestive mechanisms, if they were considered to be primary rather than reactive, appeared to be supported by the pathological findings, their mechanisms depended upon the erroneous belief that atmospheric pressure is unevenly distributed throughout the body. Not surprisingly Bert's conclusions have formed the basis for one theory of the pathogenesis of DCI involving the spinal cord.

The arterial bubble embolus hypothesis.

In 1903 Hill and Macleod observed the circulation in the vessels of a bat's wing and frog's web during and following decompression.[46] They noticed:

"For about a minute after rapid decompression the circulation continued unaltered, then small, dark bubbles were seen, first one, and then another, and then numbers scurrying through the vessels, and driving the corpuscles before them. In a moment or two the vessels became entirely occupied with columns of air bubbles, and the circulation was at an end." In 1906 Oliver confirmed these results.[47].

Apart from making considerable advances in the design of safe, yet efficient decompression procedures, Boycott, Damant and Haldane explored the possible pathogenic mechanisms of DCI.[48] They eventually selected goats as their experimental animals because they considered that they would have comparable decompression obligations with men. They studied goats which died and some that were killed at varying intervals after decompression. They noted that the presence of bubbles post mortem did not necessarily mean that bubbles had been present in vivo, because they may have formed after death. Their observations pertinent to the spinal cord were:

First, the presence of bubbles in venous blood correlated poorly with symptoms of DCI. Bubbles were found in asymptomatic animals and no bubbles were found in animals in which symptoms would have been expected had they not been killed. Arterial bubbles were occasionally seen, especially in animals that had died slowly.

Secondly, veins contained variable quantities of bubbles, but always more than arteries. Interestingly, they observed few bubbles in the veins of the brain and spinal cord.

Thirdly, they found that, as in human cases, areas of the spinal cord might be softened. The distribution of these areas of softening were most marked in, and usually confined to, the lower dorsal and upper lumbar segments and affected only white matter.

Based on these and other observations, they concluded that:

"The distribution of small bubbles in the arterial stream must be universal. They probably lodge in many places: while they are rapidly pushed forward in the grey matter and in most other tissues, if they lodge among the fatty surroundings of the capillaries of the white matter, or in actual fat, they quickly increase in size to such an extent that their removal becomes impossible.... The cause then of these areas of softening is not ordinary embolism, but embolism which becomes effective to produce infarction by reason of the effect on the size of the embolus of the local conditions of the circulation rather than from any of those peculiarities in the resistance of the different tissues to lack of oxygen, or in the freedom of collateral circulation, which determine the topography of common infarcts."

Since 1908, some experimental work appearing to support the gas embolism mechanism has appeared.[49-52] Other investigators have also observed arterial bubbles in decompressed animals.[53-55]. However, in these studies, arterial bubbles were only seen following their appearance in veins and were associated with severe DCI which was often fatal. These authors concluded that arterial bubbles were rare in less serious forms of DCI.

In none of these studies was the nucleation of gas bubbles observed directly and many of them were performed upon small rodent species that were subjected to near explosive decompression insults in order to generate an injury. As Hills reasoned,[56] it is during rapid

decompression that blood may have time to supersaturate and bubbles to nucleate between leaving the lungs and r eaching the tissues. This could result in the appearance of arterial bubbles that may be absent in the less rapid, yet spinal cord-damaging, decompressions undertaken by man.

The pathological findings in the spinal cord have been described as being compatible with ischaemic necrosis.[57,58] This has been used to support the arterial gas emboli theory.[59,60]

The development of the Doppler ultrasonic probe has resulted in a mass of evidence that intravascular bubbles are associated with DCI in both animals[55,61-65] and man.[66-73] The evidence is that bubbles first appear on the venous side of the circulation and that arterial bubbles are rare and only associated with severe disease.

A further problem with the arterial bubble embolus theory relates to the origin of arterial bubbles. It is widely recognised that, after passage through the lungs, arterial and alveolar gas tensions have equilibrated. Hills calculated that, during an ascent of less than about 6 m/min (20 fsw/min), arterial blood would not reach inert gas saturation in the time taken to travel between the lungs and tissues.[56] He noted that it is difficult to form bubbles in blood even with appreciable degrees of supersaturation and thus the formation of bubbles in arterial blood during decompression at conventional rates is most unlikely.

It is surely pertinent that arterial gas embolism from pulmonary barotrauma invariably presents with cerebral rather than spinal symptoms. DCI is common and gas embolism is rare in caisson workers and saturation divers who generally experience a controlled decompression.

It has been known for some time that arterial bubbles may arise from the paradoxical embolism of gaseous, venous emboli.[74,75] Post mortem a detectable foramen ovale (PFO) is found in about 35% of cases.[76] When accompanied by a Valsalva manoeuvre, a shunt was detectable by contrast echocardiography in 18% of adults. At rest, this figure dropped to 5%.[77] The effect of the Valsalva is important since, in the event of significant intravenous bubbling, the pressure in the right side of the heart is increased,[78- 80] which may provoke shunting in a similar manner to a Valsalva manoeuvre. Additional factors which may increase right-sided blood pressure and thereby increase right-to-left shunting in divers are: immersion, cold and negative-pressure breathing.

It has been shown that divers with a history of DCI have a higher prevalence of PFO than divers without DCI or non-diving controls.[81,82]. There has been recent interest in MRI findings in the brains of divers. One study of sports divers showed an increased prevalence of hyperintense “lesions” in divers compared with non-diving controls[83] and a more recent study has found that, in sports divers, these “lesions” are associated with a PFO.[84] None of the divers studied had had an episode of overt DCI. This has been used to imply that divers with a PFO are at a greater risk of DCI than those without.[85]. Unfortunately, the prospective trials which are required to test this hypothesis have yet to be undertaken. So far there is no evidence that a PFO is associated with lesions in the spinal cord. The argument for an embolic injury mechanism in the cord is less compelling than for the brain because the evidence is that both solid and gaseous emboli invariably embolise the latter.[86-89]

Wilmshurst has reiterated the hypothesis first proposed by Boycott et al.[48] that bubbles which embolise spinal white matter grow and obstruct the circulation whereas those which embolise the brain (or, presumably, the spinal cord grey matter) do not because of the relatively rapid washout of gas in these structures.[90] While this may occur there is, as yet, no experimental evidence to support it. The theory also does not explain the latent interval between decompression and the appearance of venous bubbles. It is difficult to reconcile this with very short-latency disease. Equally, with the spinal cord white matter having an estimated time constant of about 9 minutes,[91] this mechanism is unlikely to account for longer latency disease because the cord will have washed out its surplus inert gas by the time it is embolised. This does not mean that embolic bubbles arriving then will cause no spinal cord dysfunction, since bubble emboli are capable of disrupting the function of cords with ambient inert gas tensions.[92] It is therefore unnecessary to invoke bubble growth as a mechanism for spinal dysfunction.

Bubbles can appear in arterial blood if venous bubbles traverse the pulmonary filter. This may not occur with much frequency as the lungs have been shown to be a most efficient filter of beads[93] and gas emboli[94-98] in the size range of bubbles measured in the venous blood of decompressed dogs.[99] In the presence of massive intravascular bubbling the filtering capacity of the lungs may be exceeded.[80,96] However, this process is time-consuming[100] and accompanied by pulmonary symptoms. Thus this mechanism is unlikely to be relevant to cases of DCI where the onset occurs either during or shortly after decompression. As with other embolic mechanisms, there should be simultaneous clinical or subclinical cerebral emboli.

There is a question whether an embolic-ischaemic mechanism compatible with the pathological appearance of spinal cord DCI. There is evidence that it is the grey rather than the white matter is preferentially injured by both ischaemia[101] and emboli[92,102] although, in acute disease, the changes are subtle. The histology of spinal cords in which there was long-latency DCI (30 minutes) showed no evidence of the white matter haemorrhages which are a consistent finding in short-latency disease.[91] This indicates that the mechanisms involved are likely to be different and

possibly compatible with the minimal acute histological changes seen with ischaemia following bubble embolism.

Recently Marzella and Yin have questioned whether ischaemia playa a significant role in the pathophysiology of DCI involving the cord.[103] Using a rat model of DCI (and consequently a dive profile which would probably prove lethal to larger species), with microspheres to measure regional blood flow, they showed that lumbar spinal cord blood flow increased rather than decreased during the onset of spinal cord injury. It is unclear whether the lumbar cord in these animals was involved in the disease. Furthermore, the techniques would have been unable to detect areas of focal ischaemia which may occur in DCI. Nonetheless these results indicate that, in this model, an ischaemic/embolic mechanism is unlikely to be responsible for spinal cord dysfunction.

Other embolic theories.

End proposed that an initiating event in decompression sickness (DCS) is the agglutination of formed blood elements that lose their common revulsion by some undisclosed mechanism during decompression.[104,105] He proposed that these aggregates then act as emboli. Certainly, rheological changes in blood occur in DCI. An increased haematocrit and a loss of plasma volume are commonly found in both humans and animals with DCI.[40,78,106-110] This tends to increase blood viscosity and reduce tissue perfusion. The aggregation of blood components such as platelets[109,111-115] and leucocytes,[113] the formation of rouleaux,[108] and the finding of endothelial cell,[113,116] fat and bone marrow emboli[38,116-120] have all been described. However, these phenomena may be secondary to the nucleation of bubbles in blood or bone marrow and need not be primary events in DCI. Furthermore, the sludging of blood occurs in other conditions without resulting in the manifestations of DCI.[121] An example is disseminated intravascular coagulation (DIC) in which many of these haematological events occur on a considerable scale. However the more common consequences of DIC (haemorrhagic necrosis of the gastrointestinal mucosa, congestion of the abdominal viscera and microscopic occlusion of capillaries by thrombi with surrounding secondary, focal necrosis) are not typical of DCI. Furthermore, spinal cord involvement in DIC is most unusual.

Bubble oxygenators, part of the bypass technique for open heart surgery, impose massive rheological changes on the patient. These include the denaturation of plasma proteins, the clumping of formed blood elements and the generation of fat emboli.[123] Another complication is gas bubble embolism[124,125] which affects the brain rather than the spinal cord. Even if rheological changes were an initiating event in DCI, it is unlikely that they could account for spinal cord injury.

The dramatic improvement in DCI that is often seen with recompression, especially if applied within minutes, is difficult to explain using a theory based upon the impaction of solid emboli as the principle pathological event. If embolic phenomena are responsible for the condition, this observation would be more readily explained by compressible, gaseous emboli.

The venous infarction hypothesis.

Haymaker and Johnston raised the theoretical possibility that, under conditions of extreme DCI, bubbles in the epidural vertebral venous plexus (EVVP), combined with back pressure from bubble-laden lungs transmitted through venous anastomoses between the spino-vertebral-azygous and pulmonary vasculature, may cause venous engorgement of the spinal cord.[12] Haymaker[22] developed the hypothesis by noting Batson's observation that the EVVP is a large, valveless, low-pressure system that would make it a favourable site for the formation of bubbles.[126,127]

Hallenbeck et al. reasoned that gas bubbles are not inert in the blood stream but, as a result of a 40-100 Å layer of electrokinetic forces at the blood-gas interface, they cause structural alterations to plasma proteins.[128] This may result in the activation of the coagulation, complement and fibrinolytic cascades, the release of kinins and complex alterations to haemodynamics. They demonstrated that one of these systems, coagulation, was accelerated by the presence of bubbles.[129]

Another argument they developed was that embolic mechanisms for spinal cord injury in DCI could be criticised on the grounds that the distribution of CNS lesions appear to be unique. In other clinical, embolic conditions such as subacute bacterial endocarditis, fat embolism and mural thrombus of the left atrium, it is the brain that is the principle target organ. They quoted Blackwood's observation that arterial embolism of the cord is extremely rare. Of the 3,737 autopsies he reviewed on patients that died with neurological diseases, he found not a single case of spinal cord embolism.[130]. If emboli are responsible for the pathological findings in DCI, it is the brain rather than the spinal cord that should be preferentially embolised, since it constitutes some 98% of the mass of the human CNS and receives 75-85 times the blood flow of the spinal cord.[131] They performed a number of elegant experiments, including the direct visualisation of the spinal cord venous drainage in an animal model of DCI, that demonstrated many elements of the hypothesis that bubbles accumulate in the venous drainage of the cord and their presence, combined with their activation of the clotting mechanism, results in a slowing and eventual cessation of venous outflow. This, they observed, causes congestion and, ultimately, venous infarction of the spinal cord.[78,89,132-134] They considered that the scattered, punctate, mainly white matter haemorrhages of DCS were

compatible with Henson and Parsons' description of venous infarction of the spinal cord.[135]

This theory also has its shortcomings. First, there is some doubt that the characteristic lesions of spinal cord DCS are compatible with a venous infarction mechanism.[136] In rats, for example, obliteration of the EVVP is associated with vasogenic oedema of white matter, but not frank infarction,[137] although Martinez-Arizala et al. described haemorrhagic tissue necrosis as occurring at 24 hours and involving the grey matter more than the white.[138] Again, in monkeys, it is principally the grey matter which is involved.[139] In man, when haemorrhage in the spinal cord is associated with venous obstruction, the haemorrhage tends to be massive, centrally located, involving both the grey and white matter.[140] Venous infarction of the spinal cord is a very rare pathology[141] and this may be because the EVVP, being an extensive plexus, is difficult to obstruct. If this plexus was completely blocked at any given level, it is probable that the resulting venous congestion and infarction would be more extensive than that seen in DCI. Even obstruction at the level of the radicular veins might be expected to result in one or more lesions with a segmental distribution. Such a distribution is not typical of the lesions of DCI.

Another problem with the venous infarction mechanism relates to the frequent finding of "silent" intravascular bubbles in asymptomatic divers[67,142,143] and cases of chokes, particularly in aviators, who are free from spinal symptoms.[144] Why should "silent" bubbling, which presumably provokes similar rheological changes to symptomatic bubbling, fail to compromise spinal cord drainage? While it may be argued that such bubbling fails to exceed some arbitrary threshold, it is difficult to understand why aviators with sufficient venous bubbling to cause "chokes" do not also invariably suffer spinal cord injury.

Complement activation in DCI.

Studies in both rabbits and man show that the activation of the complement system may be an important event in the generation of the symptoms of DCI.[145-148] However cardiopulmonary bypass has been shown to activate complement in a similar manner to decompression,[149] yet without generating a syndrome similar to DCI. Furthermore, treatment of rats with a soluble complement receptor sCR-1, which has been shown to be beneficial in complement-dependent disease, failed to prevent DCI.[150] It has been claimed that variation in susceptibility to DCI in both rabbits and man correlates with the sensitivity of the complement system to activation by bubbles.[146,151]. However, others have questioned the validity of these conclusions because the extent of complement activation varies greatly over time and so predicting susceptibility to DCI on the basis of a single measurement can not be justified.[152] Furthermore, in a recent study of human repetitive dives, no association between the activation of complement in vitro and DCI was found.[153] Thus, although the activation of complement may occur in DCI, its role in the development of the manifestations of the condition is far from clear. It has never been shown how the activation of complement could result in the characteristic spinal cord lesions of DCI.

The autochthonous bubble hypothesis.

Another possible mechanism for spinal cord injury in DCI is through the liberation of a gas phase in situ (autochthonous bubbles). Indeed, it is possible to interpret the conclusions of both Boyle and Bert as proposing a role for autochthonous bubbles. However, this is rarely done. Even Boycott et al.[48] who published camera lucida drawings of a goat spinal cord showing evidence of massive autochthonous bubble nucleation, concluded that the principal mechanism involved in spinal cord injury in DCI was the embolism of arterial bubbles.

In 1916 Keyser proposed an autochthonous bubble mechanism.[154] During the discussion of a clinical case of DCI he reasoned:

"Vernon has demonstrated that fat dissolves more than five times as much oxygen and nitrogen as water.[155] The myelin of the white matter of the cord belongs to the group of fats and would, therefore, be a most common site of bubble formation in common with the fat of other parts of the body. Minute gas bubbles, which would be of no significance in the fatty tissues of the omentum or abdominal wall, would cause definite symptoms if they occurred in the cord.... From purely theoretical considerations and also the location of the lesions, it seems more probable that the bubbles form in the white matter itself rather than the blood stream."

In 1982 Hills and James, after a study of the mechanical properties of the spinal cord, proposed that spinal cord ischaemia could result if, during decompression, sufficient gas bubbles nucleate to increase spinal cord volume by 14-31%.[156] They argued that such a volume increase would raise the tissue tension sufficiently to collapse the arterioles and cut off the blood supply.

The major problem with the autochthonous bubble theory has been that, until the late 1980s, except for the observations of Boycott et al. in the goat[48] and vague references to "air lacerations"[36] or "stippling" of the white matter in early descriptions of the human pathology,[5] extravascular bubbles in the spinal cord had rarely been described. The evidence in animals was limited to the finding of bubbles scattered throughout the spinal cord white matter of six out of sixteen dogs with fatal decompression illness[41] and in the cords of decompressed fingerling salmon.[43] In man, non-staining, round spaces were

described in the cerebral and spinal cord white matter of a diver who died shortly after taking only 20 minutes to surface from a four hour dive to a depth of 40 m.[37] Numerous similar lesions were described in the cerebral white matter of two scuba divers who had apparently died prior to being brought to the surface from 42 m (140 ft). Sadly, the spinal cords were not examined.[39]

A possible reason why autochthonous bubbles have so rarely been demonstrated is that their presence in the cord may be transitory. Sykes and Yaffe examined the spinal cords of dogs that had been perfusion-fixed following recompression treatment for DCI (3 or more hours after the diagnosis).[157] Although they described abnormalities of myelin that may have been a consequence of local bubble formation, no overt bubbles could be demonstrated by light or electron microscopy.

In the mid 1980s we adapted a well established canine model of severe DCI, which had been employed for the assessment of treatments, for the investigation of the acute pathology.[158] The recording and measurement of spinal somatosensory evoked potentials (SSEP) were computerised to enable a rapid diagnosis of the onset of DCI affecting the cord. Fixation of the tissue within about twenty minutes of the diagnosis of the condition, using a rapid perfusion technique, enabled us to demonstrate very early changes.

We found that, by embedding the tissue in epoxy resin, non-staining, space-occupying lesions (NSSOL) were found at histology in the white matter of cords afflicted with DCI but not in undived controls or dived dogs with no loss of function. When paraffin wax was used as the embedding material, occasional artefactual NSSOL were found caused by the section tearing as it was cut. The size of the decompression-induced NSSOL ranged from 20 µm - 200 µm in diameter. We inferred that these lesions were likely to have contained gas in vivo because the surrounding tissue appeared to be compressed as would occur with an expanding bubble of gas. Similar findings from another canine model of DCI which employed a less stressful dive profile were reported by Burns et al.[159] They demonstrated that these lesions were gas- filled by immersion fixing the tissue in formalin at different pressures and showing that the size distribution of the NSSOL varied in accordance with Boyle's Law.

The question is how these lesions provoke tissue dysfunction. To assess this, the cords of 5 animals which had shown evidence of a loss of spinal cord function within 4-6 minutes of surfacing were rapidly fixed at the time of diagnosis (when the amplitude of the SSEP fell below 80% of baseline), but before the minimum amplitude of the SSEP was reached. This was to preserve the size of the NSSOL. From previous experience with the model[160-164] we knew that the minimum amplitude of about 20% of baseline was reached within 15-20 minutes of diagnosis, when the cords in this study would have been fixed. The cords were then serially sectioned from the conus to T12 (at which level the SSEP were measured) and submitted to computerised morphometry. Although the proportion of spinal cord white matter occupied by bubbles was small (always less than 0.5%) we concluded that autochthonous bubbles would account for the loss of cord function if between 30% and 100% of the fibres which were displaced by them were rendered non-conducting. The means whereby they might achieve this are:

1 Destruction of axons at the site of bubble formation. It was estimated that this effect would account for only 1% of the functional deficit.
2 Stretching and compression of axons around the growing bubble. This neurapraxia is an attractive mechanism because the onset is very rapid (unlike ischaemia in the cord) and reversible.[165-168] It could account for the most fulminant presentations of the condition and the improvement which is commonly seen if recompression is undertaken early or the more gradual spontaneous recovery which is often seen.
3 A biochemical insult akin to the complex interaction between blood and bubbles. If this effect were limited to those axons adjacent to the bubble surface, we calculated that this would, at most, account for 50% of the loss of function. If there is such an effect, it is unlikely to be the sole cause of the loss of function.

Another mechanism by which the cord may be injured in DCI was raised by Broome.[169] He correlated functional outcome, in pigs, with the extent of haemorrhage into the tissue, which he showed to occur after early recompression. Expanding bubbles in spinal white matter may not only disrupt axons but also the delicate microcirculation. Lacking connective tissue support, these vessels may be uniquely vulnerable to such an insult. The resulting haemorrhage can be expected to be punctate in distribution.

A degree of supersaturation is necessary to provide the number of molecules necessary for bubbles to form and grow. In a study of the spinal cords of 18 animals which were saturated for 4 hours at a fixed pressure and cardiac arrest induced prior to decompression, it was found that few bubbles formed at a saturation pressure of less than 3.6 bar, equivalent to diving to 26 m (86 ft). This indicates that bounce dives to depths much less than this are unlikely to provoke autochthonous bubble formation. The intact cord will off-gas increasingly with time following a dive. Unless bubbles form early, the probability of their formation decreases with time. In only two of our animals was the onset of spinal cord dysfunction observed more than 30 minutes after surfacing. In these, examination of the cord showed no evidence of autochthonous bubbles. The appearance of the cords in these cases closely resembled that of bubble embolism.[91]

Since the description of autochthonous bubbles in the spinal cords of canines with DCI, they have been found by other investigators[170,171], although in the first of these studies the number found was not considered to be sufficient to account for the observed loss of function.

Conclusions

1 Given the range of latency of onset of spinal cord injury in DCI from during decompression to as long as 48 hours after surfacing, it is most unlikely that any single mechanism will apply in all circumstances.

2 The onset in fulminant cases, which tend to occur after deeper dives, requires a local mechanism which rapidly interferes with white matter conduction. Autochthonous bubbles meet these requirements.

3 A purely embolic mechanism is an attractive explanation for cases in which the onset is delayed by a few minutes after completing the decompression (perhaps 10-20 minutes, or 1-2 time constants of intact spinal cord gas exchange) or which arise from dives to less than about 25 msw. The mechanism of amplification of embolic bubbles by the diffusion of excess tissue gas, as proposed originally by Boycott et al., although lacking direct experimental evidence, may occur slightly earlier than this, particularly in divers with significant right-to-left shunting through a PFO or other atrial septal defect.

4. The role of the venous infarction hypothesis is unclear. It is unlikely to provoke a fulminant loss of function requiring, as it does, obliteration of most of the flow in the epidural vertebral venous plexus, which appears to take time. The role of this mechanism in cases with a delayed onset will be determined only when the pathology of that presentation is clearly defined as the histology of venous infarction and spinal cord gas embolism are quite distinct. The evidence, from only two experiments reported by Francis,[91] is that, in his model, an embolic mechanism was likely to be responsible for loss of function 30 or more minutes after surfacing from the provocative dive.

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