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Decompression Sickness in Divers


# Pathological Aspects of Decompression Sickness

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## Abstract

Recent studies concerning the pathogenesis of decompression sickness (DCS) were reviewed. Discussion of the related evidence linking the observations of pathological findings in human beings and experimental animals with acute DCS leads us to conclude that the acute elevation of tissue pressure inside a compartment such as a bone marrow cavity which is encased by rigid cortical bone, following acute decompression of atmospheric pressure is most responsible for the development and progression of tissue damage in DCS. The brain and the spinal cord are also located within compartments which are encased by a rigid dural membrane with or without an overlying rigid bone. A high incidence of damage of all of these three organs is seen in patients with acute DCS. However, the severity of tissue damage is not equally distributed throughout a compartment, and cannot be understood only by this etiology. Instead, "watershed zones" may explain the site predisposition of tissue damage in each organ. "Watershed zones" are the most vulnerable areas where the arterioles and arteries may easily collapse due to the acute increase of the perivascular tissue pressure.

Abnormalities of the venous vessels are widely observed in these three organs in DCS, which are characterized by many nitrogen gas bubble emboli, fat emboli and thrombi in the venous system. These abnormalities in the venous system should cause disturbances in venous blood circulation. Disturbance in venous blood returning towards the heart from these organs should accentuate the elevation of the tissue pressure inside the compartments. The disturbance of the venous system may not be the last word when discussing the pathogenesis of tissue damage in DCS, but it should be considered in any further research on this subject.

## Introduction

For many years, it has generally been accepted that the creation of intravascular gas bubbles resulting in bubble embolism in arterial system is the most important aspect for the pathogenesis of DCS. Since 1950's, however, many biophysiological phenomena which are unexplainable only by the arterial bubble embolism have been observed by many investigators. Arterial bubble embolism cannot explain why (1) some DCS patients do not recover from the disease in spite of an adequate recompression therapy; (2) the administration of anticoagulants such as heparin is sometimes very effective for the disease; (3) obese or fat persons are more likely to suffer from DCS as compared with thin persons; and (4) clinically, the spinal cord is much more frequently injured than the brain.

Aseptic necrosis of long bones and damages in the central nervous system (CNS), e.g. brain and spinal cord, in association with DCS are still major problems in both amateur and commercial diving using compressed air.

This paper is a review of recent works on pathogenesis of DCS, specially focussing on the etiological aspects of bone necrosis and damage in CNS.

## Bone Necrosis In DCS (Dysbaric Osteonecrosis)

Dysbaric osteonecrosis (DON), a type of aseptic and avascular necrosis of long bones, especially the femur, is relatively common in divers (Davidson, 1976; Kawashima, 1976). DON has been generally thought to occur as a result of nitrogen gas bubble formation during the decrease of atmospheric pressure (decompression), because of the greater solubility and higher affinity of nitrogen gas to bone marrow, especially its large amount of fatty tissue. Probably the largest series of DON cases was reported from Japanese divers (Kawashima, 1976). DON has become also a serious socio-economic problem among them.

DON is unquestionably preceded by bone marrow necrosis associated with the acute phase of DCS (Kawashima et al, 1977). Thus to understand the development and progression of DON, it is most important to understand the etiology of bone marrow necrosis. Bone marrow is confined within the rigid boundary of cortical bone which forms a compartment, that is a bone marrow cavity. Needless to say, cortical bone is particularly noncompliant, and in the range of physiological pressures, enveloped bone marrow is difficult to be distended in both the longitudinal and circumferential modes. Thus, the cortical bone boundary can provide a rigid outer casing against which bone marrow, enlarged by increase of the nitrogen gas inside the fat cells, can no longer expand without greatly elevating the force it exerts upon the cortical bone and, hence, without substantially elevating the pressure within the bone marrow itself (Lanphier et al, 1990; Lehner et al, 1990; Kitano et al, 1994).

With an increase of the atmospheric pressure (compression), nitrogen gas enters the blood circulation via the alveolar walls of the lung, followed by an elevation of blood pressure and secondary tissue pressure until a new physical situation equivalent to the atmospheric pressure is reached. The high affinity and great solubility of nitrogen gas to lipid or lipoid substances permit the gas to easily and quickly enter into the fat cells until a new equilibrium is reached.

The relationship between the tension of the vascular wall and intravascular blood pressure can be describe as:

$$T=rP \text{ (Laplace's law)}$$

where T is tension of the vascular wall; r is 1/2 of the diameter of the blood vessel; and, P is the blood pressure inside the vessel.

Transient elevation of blood inside the vascular channels greater than the tension of the vascular wall may occur by compression. However, tissue pressure elevation may occur soon after, such that the vascular wall may return its almost normal tension. This means that the blood circulation can be maintained at almost physiological state even in the compression phase during the increase of atmospheric pressure.

With the decrease of atmospheric pressure during decompression phase, nitrogen gas inside the tissue leaves the tissue and enters the blood circulation system. Intravascular gas can be removed vta the pulmonary alveoli. At first, blood pressure decreases with the descent of the atmospheric pressure and secondly tissue pressure decreases. However, as nitrogen gas has a high affinity to and a great solubility in fatty tissue, the egress of nitrogen gas from fatty tissue may be markedly slower than from non-fatty tissue and retard the decrease of pressure in fatty tissue (Bove, 1977). Figuratively speaking, fatty tissue shows an 'increase' in tissue pressure in the decompression phase (Lehner, 1990).

In the bone marrow cavity this condition may be exaggerated. Nitrogen gas cannot

easily leave the bone marrow because it is: (1) a fat cell-rich tissue; and (2) located in a compartment encased by a non-compliant boundary bone. As a result of the marked retardation in the decrease of bone marrow pressure, bone marrow pressure often exceeds the blood perfusion pressure. An increased resistance to intramedullary blood flow could account for the collapse of the vascular walls (Lehner, 1990).

The next problem for discussion here is that nitrogen gas bubbles which may create in intra- and extravascular spaces during decompression. The formation of extravascular gas bubbles should directly result in the destruction and alteration of cells and intercellular tissue matrices, to some degree. Fat embolism, which has been widely observed in the cadavers of DCS victims seems caused by fat cell disruption by direct mechanical stress of nitrogen gas bubble formation in their cytoplasms (Haymaker, 1957; Kitano and Hayashi, 1981).

Nitrogen gas when soluble in water can be regarded as an incompressible hydraulic substance for transmitting pressure. It can diffuse out of the cortical bone boundary into the periosteal soft tissue layers under the increased pressure, although it is not acceptable if nitrogen gas can sufficiently escape from the bone marrow cavity. When nitrogen gas bubbles are created in the bone marrow, they can no longer hydromechanically pass through the cortical bone boundary. Thus the retardation of descent of the intraosseous bone marrow pressure should be exaggerated. Again figuratively speaking, "elevation" of the intraosseous tissue pressure should be exaggerated.

It has been widely accepted that the intravascular gas bubbles injures the endothelium of blood capillaries and venules (Warren, 1973), and they activate the blood coagulation system causing thrombus formation around the gas bubbles (Philp, 1972; Kitano et al, 1978; Kitano and Hayashi, 1981). This should lead to nitrogen gas bubble lodgement in the vasculature causing disruption of blood flow (Fig. 1).

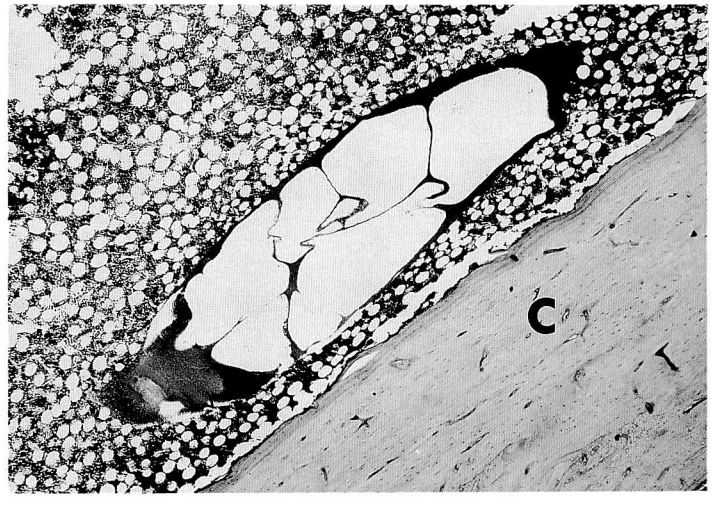


Fig. 1. Multiple nitrogen gas bubbles in a sinusoidal lumen of the femoral bone marrow of a rabbit with experimentally induced DCS. Each bubble is surrounded by a membraneous thrombus (hematoxylin-eosin staining, C: cortical bone).

As for the mechanisms for bone marrow damage from hyperbaric exposure, the venous system must be discussed (Kawashima et al, 1977; Kitano et al, 1978, Kitano and Hayashi, 1981). Occlusion of the venous drainage of bone by gas bubbles with or without fat emboli and thrombi is known to slow down or stop arterial circulation to the region drained by the occluded veins via back pressure (Bove, 1977).

The main pathway, perhaps the only route, of dissipation of the elevated intraosseous pressure, should be the blood vessels. If the gas bubbles, fat emboli and thrombi are widely retained within the bone marrow vasculature, the descent of the intraosseous bone marrow pressure will not occur and will result in the collapse of the blood vessels of both the arterial and venous systems (Fig. 2). The possibility of injury due to anoxia of the tissues and cells will be exaggerated also through these changes in bone marrow vasculature.

As for the vasculature, blood vessels with lower blood perfusion pressure should be more affected than those with higher perfusion pressures from elevated extravascular tissue pressures. This means that the collapse will more easily occur in intraosseous blood vessel walls ranging from the sinusoids, blood capillaries, arterioles, smaller arteries, and larger arteries. Moreover, the distribution of pressures in a blood vessel is not constant through out its length. Poiseuille's law states:

$$v = \pi r^4 / 8 \mu l \times \delta p$$

where v is the volume of blood flow, $\pi$ is circular constant, r is 1/2 of the diameter of the vessel, $\mu$ is the viscosity of fluid, l is length of the vessel, and $\delta p$ is the blood pressure differential. According to this law, the blood pressure in the proximal section of the vessel is

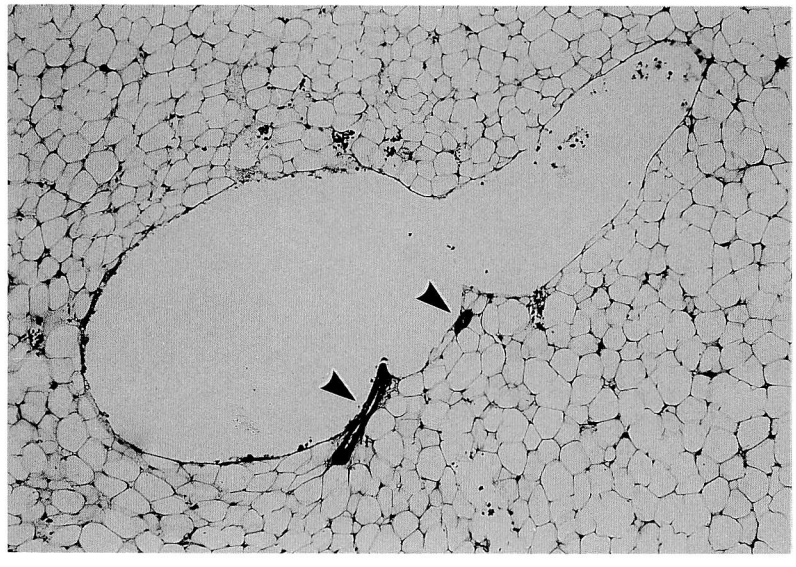

Fig. 2. Collapsed arterioles (arrow heads) of the femoral bone marrow of a rabbit with experimentally induced DCS. The collapsed arterioles are located just in vicinity of a dilated sinusoid possessing a nitrogen gas bubble, however, most vascular vessels show the tendency of collapse, in more or less marked degree in the bone marrow cavities of experimental animals (hematoxylin-eosin staining).

higher than that of the distal portion. This means that the areas which are supplied by distant arterial branches are more likely to be injured than those which are supplied by proximal arterial branches (Kitano et al, 1994).

A detailed analysis of bone circulation is provided in various textbooks. Brookes (1971) described three different circulations for long bones. The epiphysis is supplied by extraosseous arteries which penetrate the bone at the epiphyseal region. At present there is little evidence that epiphyseal arteries anastomose with medullary arteries in either growing or mature bone, although there are some data to support the existence of such anastomoses. These vessels are usually considered as end arteries which anastomose minimally within the bone.

Brookes also described a number of vessels that penetrate the metaphyseal region directly and lie transversely in cancellous bone of this region. The arterial branches of the metaphyseal region are known to anastomose, and a significant degree of vascular occlusion would therefore be necessary to cause metaphyseal ischemia.

As for the diaphysis, intraosseous arteries are composed of branches of the one or, if present, small numbers of nutrient artery (ies) which enter (s) the nutrient foramen (-mina). They are mainly arranged in longitudinal directions towards both the proximal and distal ends. So, while the portion near the nutrient foramen maintains a relatively high blood pressure, the portion distant from the foramen has relatively low pressures.

Recently, we employed the term 'watershed zone' which has been widely and extensively used in the field of neuropathology into the etiology of DON (Kitano et al, 1994) when considering the mechanisms for bone marrow ischemia from hyperbaric exposure. A watershed zone is a boundary zone between territories of major arteries in CNS, and is a region vulnerable to ischemia (Wodarz, 1980; Carpenter, 1983). This zonal pattern of ischemic CNS damage is usually seen after a conscious subject has collapsed as a result of some sudden reduction in cardiac output, or when an episode of anoxemia or hypoxemia has led to a secondary depression of the myocardial function. As a consequence of a sudden fall in blood pressure, a characteristic feature of localized CNS necrosis in the watershed zones between major arterial territories can be recognized.

We applied this term 'watershed zone' to specific areas of the bone marrow of femur. The most conspicuous watershed zone in the femoral bone marrow is the distal shaft area (Fig. 3). We also used this term for certain areas such as the weight-bearing juxta-articular area. This area is considerably distant from the nutrient formen (-mina) and is supplied only by the end arteries which do have no significant anastomosis (Fig. 3).

Although it is easy to envisage that a large amount of gas can result in the total bone marrow necrosis of the long bones including the femur (Kitano and Hayashi, 1981), bone necrosis often does not occur equally throughout the whole length of long bone, because: 1) not all nitrogen gas is formed equally in various sites of the bone marrow in proportion to distribution of fat cells and hematopoietic cells; and 2) where the blood perfusion pressure decreases in the watershed zones, it can generate enough differential to cause blood flow to cease. For lesser amounts of gas, therefore, the closure of arterial system can be localized, depending upon whether or not the tissue pressure exceeds the blood perfusion pressure. As for human femoral bone marrow, both the weight-bearing juxta-articular area and distal shaft area are watershed zones (Kitano et al, 1994), and both areas show characteristically a high incidence of DON in divers (Kawashima et al, 1978).

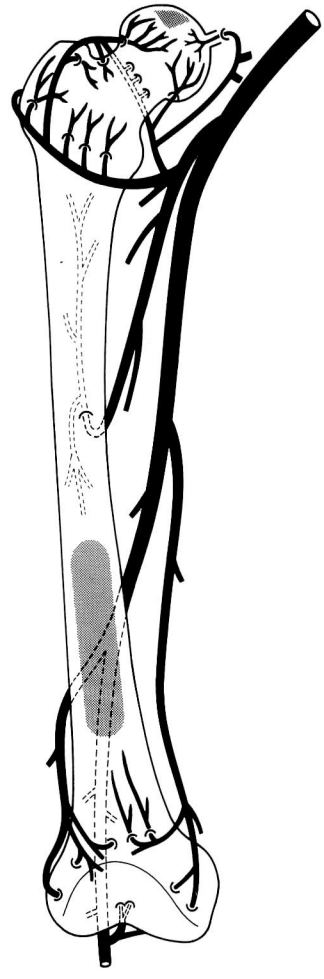

Fig. 3. Schema of 'watershed zone' of the bone marrow of human femur.

## Damage of the Central Nervous System (CNS)

*1. Spinal cord damage*

Hayashi (1976) reported that 27.3% of all cases of acute DCS due to diving manifested some spinal cord dysfunction. By contrast, the incidence of cases showing cerebral dysfunction was only 1.1%. Historically the spinal cord appears to be clinically involved in DCS more frequently than the brain (Hallenbeck, 1975).

The pathogenesis of spinal cord damage in DCS has been a subject of controversy, despite the extensive and exhaustive works on the histopathological analysis on spinal cord damage in DCS (Haymaker, 1957; Kitano et al, 1977; Palmer et al, 1976; 1978). These studies provide evidence that gas embolism within either arterial or venous channels may play an important role in the development and progression of the spinal cord damage. As described above, a high inert nitrogen gas concentration in lipid- and/or lipoid-rich tissues including CNS, the bubble emboli may grow sufficiently large enough to obstruct microcirculation (Francis et al, 1988; 1989). Such a mechanism would adequately explain some of the histopathological

features of spinal cord damage in DCS, but simple obstruction of the microcirculation is inadequate to explain site predisposition in spinal cord damage. Many investigators have already noted that the white matter, especially the lateral and posterior funiculi of the upper thoracic segments of the spinal cord are the most vulnerable to DCS (Hayashi, 1974; Kitano et al, 1977; Hills and James, 1982; Francis et al, 1988; 1989) (Figs. 4 and 5).

That the dural membrane is noncompliant has already been confirmed by many investigations (Hills and James, 1982). Thus, the dural membrane can provide an effectively rigid outer membrane encasing a compartment of spinal cord parenchyma. Hence, in this compartment the spinal cord can not expand, thus the spinal cord will exert pressure against the dural membrane as the result of internal (either intravascular or extravascular) nitrogen gas bubble formation.

With a decrease in the atmospheric pressure, the volume of nitrogen gas bubbles, when formed and separated from blood, tissue fluid and lipoid-rich matrices of the spinal cord can not be dissipated through the dural membrane. With encased gas bubbles, extravascular pressure must exceed the perfusion pressure of the blood within, causing arterial and/or arteriolar collapse with subsequent impairment of local circulation resulting in tissue anoxia. The corresponding values of the blood perfusion pressure in the spinal cord are likely to be appreciably lower, especially in the watershed zones which are vulnerable to ischemia. In the spinal cord, the watershed zones must be viewed in two ways. One is that in the transverse planes

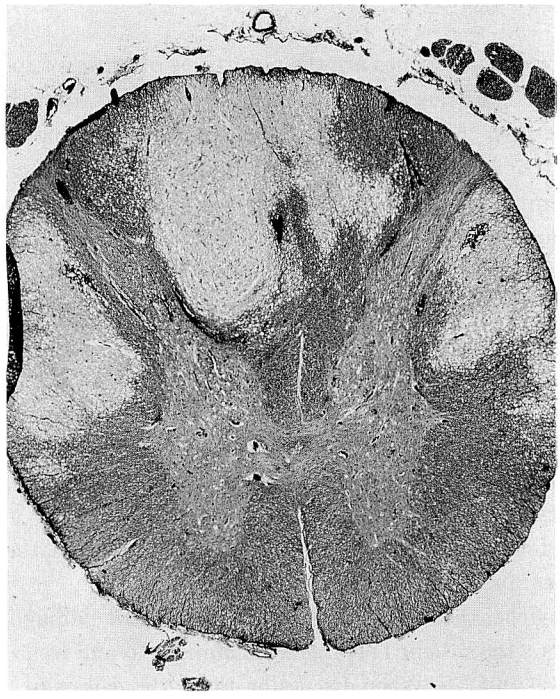

Fig. 4. Edematous necrosis of the lateral and posterior funiculi of a thoracal segment of the spinal cord of a 36-year-old male diver who died 5 days after the onset of acute DCS (hematoxylin-eosin staining).

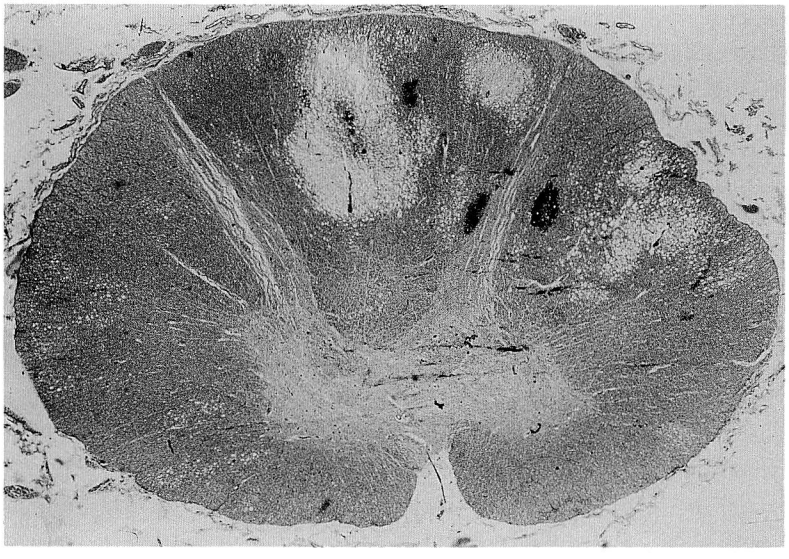

Fig. 5. Edematous necrosis of the lateral and posterior funiculi of a cervical segment of the spinal cord of a 20-year-old male diver who died 15 days after the onset of acute DCS (hematoxylin-eosin staining).

of the spinal cord the watershed zones are the territories of anterior, posterior and radicular arteries (Hassler, 1966). The other is that in the horizontal direction the watershed zones are the boundary zones between the two groups of nutrient arteries, one from the head and neck region, and the other from the abdominal region (Adamkiewicz). It can be argued that gas bubbles separated from the spinal cord parenchyma upon decompression are sufficient to cause the collapse of arterioles and to cut off the blood flow at the watershed zones (Hills and James, 1982). From a clinical standpoint, this can explain the predominant involvement of the watershed zone at the upper thoracic segments in spinal cord damage in DCS, as these segments have low perfusion pressures (Hayashi, 1974; Hills and James, 1982). This is also consistent with another relevant finding, that the histological sections of spinal cord with DCS in the transverse plane there are vulnerable areas such as lateral and posterior funiculi (Kitano et al, 1977); these funiculi have the lowest perfusion pressures.

It is easy to envisage how large amounts of gas could cut off blood flow from all arterioles, resulting in occasional total paralysis. For lesser amounts of gas, however, the closure of arterioles could be localized, depending upon whether or not the gas had been formed to produce the hemiplegia often observed in divers.

As a whole, the neuropathological aspects of spinal cord damage in DCS are also too numerous to discuss, but the salient features seem similar to and well compatible with those of bone marrow necrosis in DCS. When discussing the pathogenesis of spinal cord damage in DCS, we must be concerned with three subjects; the compartment encased by the dural membrane, the lipid and/or lipoid content of the spinal cord parenchyma and also the arterial and arteriolar distribution in and around the spinal cord.

*2. Cerebral damage in DCS*

As already mentioned, one of the principal reasons why Hallenbeck et al (1975) and Kitano et al (1977) argued against arterial gas embolism as the mechanism for spinal cord damage in DCS was because the spinal cord appeared to be clinically more frequently involved in DCS than the brain. This is the reverse of what would be expected based on the distribution of blood flow and nitrogen gas emboli. For gas embolism to be the mechanism for CNS damage in DCS it would be necessary to postulate extensive yet clinically silent cerebral injury. With the use of modern investigative techniques, evidence is now emerging that the brain can be involved in DCS to a greater extent than is apparent from clinical examination alone (Adkinson et al, 1989).

A histopathological analysis on four brains obtained from acute DCS victims showed more or less marked cerebral damage in all the four brains (Kitano et al, 1990; 1991). One of the commonest findings was that numerous microspots of necrosis were present around the blood capillaries and venules in the deeper cortex and superficial white matter (Fig. 6). The size and location of the spots suggest that very small nitrogen gas bubble emboli were trapped. Intravascular nitrogen gas bubbles may increase vascular permeability through damage of blood-brain barrier due to intimal cell injuries by direct mechanical action and by indirect effects of bubble-blood interaction. The bubble-blood interaction includes the alteration of configurations of blood proteins which leads to an aggregation of blood platelets, activation of the blood clotting system, release of vasoconstrictive substances and release of substances injurious to vascular endothelium. Increase of the alteration of the vascular endothelium results in an increase of permeability of blood-brain barrier, causing edema, plasma exudation, hemorrhage and parenchymal damage. Chryssanthou et al (1977) were the first to observe experimentally an increase in the permeability of the blood-brain barrier after de-

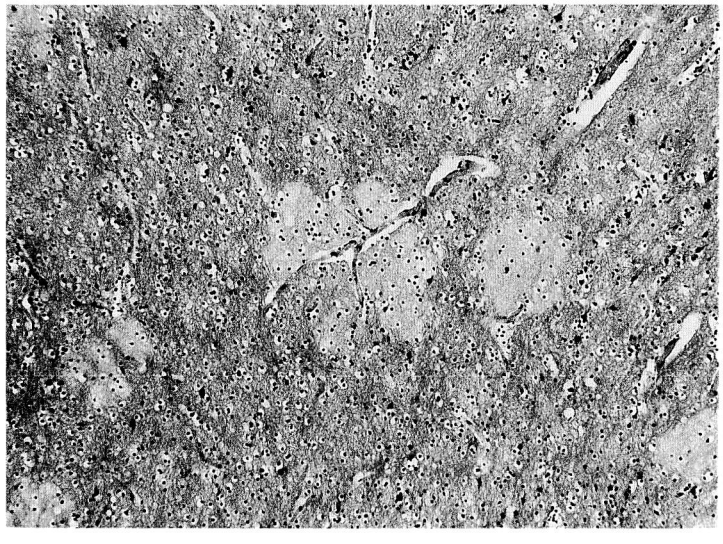

Fig. 6. Spotty foci of necrosis in the deeper gray matter of the cerebrum of the same case of Fig.4. The spots are located around blood capillaries (hematoxylin-eosin staining).

compression. Hills and James (1991) demonstrated it, by injections of microbubbles to the unilateral carotid arteries in the experimental animals. Palmer, et al. (1992) also found such microfoci of acute necrosis in the gray mater of the brain of a diver who died of acute DCS. They stated that the formation of microfoci of acute necrosis in the gray matter might be the creation of nitrogen gas bubbles.

The recent studies provide evidence that nitrogen gas bubble embolism may play an important role in the pathogenesis of cerebral damage in DCS. To this date, however, the role of bubble emboli in endothelial barrier disturbances for tissue damage of the spinal cord, bone marrow, or others in DCS has not been made clear unlike brain studies, although bubble emboli are distributed to all tissues and organs of whole body (Kitano et al, 1977; Francis et al, 1989).

Our analysis disclosed another unusual but very important feature in one of the four brains. In addition to thrombus formation in the veins at the deep layer of white matter of the cerebrum associated with lodgement of nitrogen gas bubbles, there were also multiple foci of edematous necrosis at the deep layer of the white matter, especially at the periventricular areas of the cerebrum (Kitano et al, 1990; 1991) (Fig. 7). Such a characteristic cerebral lesion had not been reported before. We mentioned that the anatomical localization

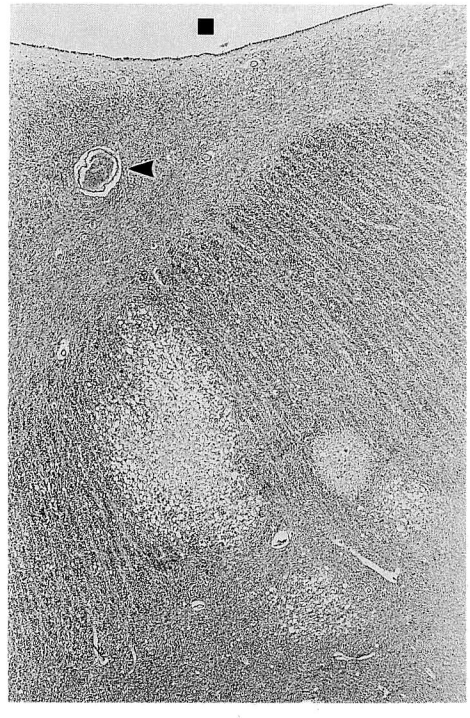

Fig. 7. Foci of edematous necrosis of the periventricular, deep white matter of the cerebrum of the same case of Fig. 4 and 6. (hematoxylin-eosin staining, dark square: lateral ventricle, arrow head: vein with erythrocytic stagnation).

of the necrotic foci was in watershed zone (Wodarz, 1980). The conclusion of our paper was that intravascular nitrogen gas bubbles associated with thrombosis accelerate the retardation of venous blood flow, with a subsequent increase of the tissue pressure and intimately contribute to the formation of the necrotic foci in the watershed zone(s) of the brain in this case with acute DCS.

For now, we must point out that the brain is also composed of lipid- and/or lipoid-rich tissue, and also encased by a noncompliant dural membrane which is also closely overlined by a specially noncompliant rigid cranial bone. Both the dural membrane and the cranial bone provide a compartment for the brain. During decompression, the encased cerebral tissue pressure has the potential to exceed the blood perfusion pressure with subsequent vascular collapse resulting in tissue anoxia. From a physio-anatomical view point, the watershed zones are easily damaged by the abnormal internal tissue pressures as these zones have low blood perfusion pressure and high nitrogen content resulting from the high content of lipid and/or lipoid.

## Conclusion

The details of DCS are too numerous to discuss here, but the most salient and commonest aspect of bone marrow necrosis, spinal cord damage and cerebral damage in DCS is that these three organs are all located within a compartment encased by noncompliant materials such as bone, dural membrane or both. Also noteworthy is that these three organs and tissues are rich in the content of lipid and/or lipoid which show a great solubility of and a high affinity to nitrogen gas. During decompression the encased tissue pressure has a potential to exceed the vascular perfusion pressure mainly due to retardation of nitrogen gas with or without gas bubble formation from the lipid and/or lipoid substances. When gas bubbles are created, the elimination of the bubbles should be very difficult. Subsequent collapse of the vasculature, even of the arterial system takes place, especially at the watershed zones. Unquestionably the collapse of the arterial system causes tissue anoxia resulting in tissue damage.

Previously, in analyzing the pathogenesis of DCS we have paid too much attention to disturbances in venous blood returning towards the heart. We have proposed a "venous return disturbance theory" because there were many gas bubbles with or without associated thrombus formation within the venous system (Hayashi, 1974; Kawashima, 1976; Kawashima et al, 1977; Kitano et al, 1977; 1978; 1991; 1992; Kitano and Hayashi, 1981). But now, we should like to revise our opinion. It seems more appropriate to consider that the main pathway of dissipation of the elevated internal tissue pressure should be the blood vessels, especially of the venous system, until the internal tissue pressure becomes equivalent to the surrounding organs and tissues. Thus, the retention of nitrogen gas bubbles widely within the venous system will not allow the decrease in pressure of the encased tissues and organs.

According to Lehner (1990), we must now employ the 'compartment syndrome theory' to explain the pathogenesis of bone marrow necrosis, spinal cord damage and cerebral damage in DCS, with careful regard to 'watershed zones'. However, while our 'venous return disturbance theory' may not be the last word on the subject, it should be considered in any further investigations.

## Acknowledgement

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