HAEMOSTASIS, DECOMPRESSION SICKNESS AND MIGRAINE

JF Cleland

INTRODUCTION

There is no doubt that decompression sickness (DCS) is largely due to widespread direct and in direct tissue disruption as a consequence of bubble formation and vascular block. There is however, a wide and complex range of patho-physiological events which follow the formation of intravascular bubbles and how much these events influence the severity and course of the disease, is not known. However, it is generally accepted that not all of these subsequent events are protective, and indeed some, particularly activation of the haemostatic process and aggregation of platelets at the blood bubble interface, are almost certain to contribute to the problem.

The evidence for involvement of the haemostatic mechanism in DCS is convincing and in fact one could argue that it would be unphysiological for the haemostasis mechanism, platelets in particular, not to respond to the formation of intravascular bubbles with in addition, varying, direct endothelial and other tissue injury. Actually, it would appear that intravascular bubble formation and endothelial damage are not necessary for platelets to aggregate as ex vivo experiments show that platelets will aggregate with decompression stress alone. In addition to these mechanical events, there are other factors important in the pathogenesis of DCS which could operate through activation of the haemostatic mechanism. These include strenuous exercise to the level of exhaustion, fear and hypoxia. The real question is how important is this triggering of the haemostatic mechanism? Does intravascular coagulation provoked by bubbles lead in itself to further significant ongoing tissue injury? If so, there would be three main implications:-

(i) Anti-haemostatic drugs might be helpful in the management of DCS.

(ii) Such drugs may be helpful in the prevention of DCS.

(iii) People with an already hypersensitive or activated haemostatic mechanism could be recognised who could be assumed to have a high risk of DCS with any given decompression stress.

We have now had a decade of diving experience since it was recognised haemostasis might play a part in DCS and in spite of very significant advances in our understanding of the physiology of haemostasis, particularly the role of prostaglandins in platelet function over this period, the literature contains a surprisingly small amount of published related biomedical research. When I reviewed this subject in 1976, I predicted (on the basis of my haematological bias of course), haematological management would be almost as important as recompression. Antiplatelet drugs would provide cheap, at least partial, protection, and we would be able to recognise with blood tests high risk divers with various clinical conditions and advise them accordingly. In contrast it seems any advances in this area have not been translated into practical benefit for us, either as doctors or divers.

I will review these three main areas in turn.

THE USE OF ANTI-HAEMOSTATIC DRUGS IN THE TREATMENT OF DCS

As far as I am aware no drug or combination of drugs has been shown to be safe and effective for the treatment of DCS by controlled double blind studies in humans. It also seems unlikely that such studies will be forthcoming with the fortunately infrequent occurrence of severe DCS usually in remote locations. The usual consequence is delayed treatment which in itself, with established and irreversible ischaemic tissue injury, gives any anti-haemostatic drug little chance of providing benefits. In addition, there are obvious potential hazards in the use of such drugs. Particularly bleeding which must be weighed against their potential benefit.

Dextran

Apart from its obvious potential benefit as a volume expander both dextran-40 and dextran-70 would be expected to have an additional benefit as the result of their antiplatelet action. In spite of this, there seems to be no evidence that dextran therapy has any advantage over simple fluid replacement.

Heparin

Heparin cannot yet be considered to be of predictable consistent value in the treatment of DCS. A few individual case reports suggest a significant benefit and there are a number of animal experiments in which heparin has reduced mortality from decompression sickness. However, other studies, in experimental animals, particularly dogs, have failed to confirm the benefits and concern has been expressed at its use as it is suggested that haemorrhage may play an important role in the pathogenesis of inner ear decompression sickness. In causing haemorrhage into ischaemic areas, particularly the spinal cord, it could aggravate neurological deficits. As I understand it, heparin is only recommended in severe cases of pulmonary DCS unresponsive to recompression therapy.

Antiplatelet Drugs

The role of antiplatelet drugs in the treatment of DCS remains uncertain. There appear to be very few studies in which antiplatelet agents have been used to treat decompression sickness. Prostacyclin, nature's most potent, though short-acting, inhibitor of platelet aggregation, has now been available for approved experimental use in humans for some years. In addition to its potent anti-aggregatory effect, it is also a potent vasodilator, and might be expected to be of benefit in DCS, particularly if used early. I have found only one reference to its use when it was used in association with indomethacin and heparin in dogs with experimental central nervous system ischaemia after air embolism. Neuronal recovery was promoted. Prostaglandin E1 has been used for therapy of DCS in dogs without beneficial effect.

THE ANTI-HAEMOSTATIC DRUGS IN THE PREVENTION OF DCS

Heparin

Studies on the prophylactic use of heparin in experimental animals have been contradictory, some

showing significant protection others showing no benefit. Owing to differences in administration, subcutaneous or intravenous and the timing of the treatment, this drug is not really a practical prophylactic in the human.

Oral Anticoagulants

There is little experimental support for use of prophylactic oral anticoagulants, which have not been found to have a consistent protective effect in experimental animals.

Antiplatelet Drugs

Because of the ease of administration, prolonged affect, safety and low cost, antiplatelet drugs are an attractive proposition for the prevention of DCS. Drugs which have been investigated include aspirin, dipyridamole (Persantin), aspirin in combination with dipyridamole, and aspirin has also been used in combination with levodopa.

Aspirin

Some studies in man have been unencouraging, in showing little protective benefit as measured by platelet survival times and post dive platelet levels. Aspirin given shortly before a dive has also been shown to have no affect on occurrence of DCS. Prophylactic aspirin has also been shown to have no effect in protecting rats from DCS. However, pre-treatment with aspirin for thirty days has been shown to significantly decrease clinical signs of serious forms of DCS in rats, and when used in combination with levodopa this benefit was even more striking. This combination of drugs reduced the mortality of rats from 31% to 5.6%. It may be that aspirin could have a significant benefit if used in an appropriate low dose for a longer period before diving. Although the risks of aspirin ingestion are very small, there remains some theoretical concerns about its widespread use. The prevalence of minor haemostatic disorders, such as Von Wille brands disease, in the community is known to be much higher than previously recognised and it is known in such patients who have a minor or negligible haemostatic defect aspirin can significantly aggravate the problem. Such patients could be at excess risk in diving, particularly in bleeding from mucosal surfaces, eg. nasal passages with mask squeeze etc.

Dipyridamole (Persantin)

Used alone, little practical benefit has been demonstrated even on platelet kinetics let alone clinical signs of DCS.

Aspirin and Dipyridamole

Used in combination, these drugs have been shown to have a synergistic effect on platelet function and this had led to their use in combination in a number of clinical settings, eg. prosthetic heart valves. This combination has been shown to eliminate the immediate post dive fall in platelet survival time but whether this necessarily implies a benefit is uncertain. Other drugs, dipyridamole derivatives, have been used prophylactically in human divers and shown to prevent a post decompression fall in circulating platelet count. Prophylactic use of these drugs has also been shown to significantly decrease the incidence and severity of bends in rats compared with unprotected controls. Once again the significance of these observations for the prophylaxis of clinical DCS in the human remains uncertain.

RECOGNITION OF HIGH RISK GROUPS FOR DCS

Many clinical groups are known to have excess risk of decompression sickness for given decompression stress. These include women, who have more than three times the risk of males, obese people, and unfit and older divers. Whether this excess risk in any way relates to haemostatic variables is not known.

There are an increasing number of disorders being recognised in which there are specific inherited or acquired abnormalities in the haemostatic mechanism either involving platelet function, coagulation factors, coagulation inhibitors or components of the fibrinolytic system. Such disorders, “thrombophilias”, are characterised clinically by a tendency to thrombosis, usually venous, less commonly venous and arterial, and these disorders include antithrombin III deficiency, protein-S deficiency, protein-C deficiency, heparin co-factor II deficiency, and the presence of the lupus anti-coagulant. Collectively however, these disorders are still extremely uncommon and the diving medical could well identify such patients from the past or family history of thrombotic problems, recurrent abortions, etc. On theoretical grounds such patients would be at excess risk of DCS given any decompression stress, but to identify them routine detailed tests of haemostasis could not be justified.

ORAL CONTRACEPTIVES

Thrombotic complications of oral contraceptives have lessened considerably with the use of preparations containing smaller doses of oestrogen or progestogen only preparations. A few studies of female divers taking oral contraceptives have been reported, and no excess risk of clinical DCS has been shown. On theoretical grounds at least however, I believe would be most unwise for a woman on oestrogen-containing oral contraceptives to engage in “aggressive” diving.

MIGRAINE

It has been generally accepted that migraine can be aggravated by diving. It is also generally accepted that migraine is a relative or absolute contra-indication to diving for the reason that its associated neurological symptoms and signs overlap with those of DCS creating confusion in diagnosis.

Documentation of the association of migraine headache with diving is hard to find. In 1944, one report describes 155 medical and university students who were exposed to low pressure, 30,000 to 38,000 feet in hypobaric chambers. Sixteen of these students reported scotomata and headache, and out of these 16, 11 had a history of previous migraine. It was concluded that people with migraine are more likely to get headaches when they undergo barometric change. A subsequent study in 1965, also involved medical personnel, three doctors and one nurse who were subjected to compression to 66-135 feet below sea level. All four experienced scotomata and head ache and developed abnormal EEGs, and of these four, three had a history of previous migraine.

By what mechanism could migraine be precipitated by diving? The evidence is that the association almost certainly has its base in platelet behaviour.

Following the early observation that platelet micro-aggregates are present in the circulation of patients with migraine headache, evidence for abnormal platelet function in patients with migraine emerged during the early 1970's. Initially there was uncertainty as to whether these micro-aggregates were the result of migraine or a major or contributing cause. It has now been shown that such platelet micro-aggregates are also present in the prodromal periods of migraine. And between migraine attacks platelets have been shown to be abnormally sensitive to platelet aggregants such as 5HT and ADP and in addition, platelet enzyme defects have also been reported in migraine sufferers. When platelets are activated and they aggregate in vivo, the contents of the beta granules are released, the so called "release reaction", and this includes the release of beta thrombo-globulin and platelet factor IV. Patients with migraine, both in between and during attacks, have been shown to have increased beta thrombo-globulin levels with the highest levels during attacks. Not all patients, in fact 25% of patients only in one study, show increased beta thrombo-gobulin levels and it seems that patients with classic migraine are more likely to show evidence of abnormal platelet turnover (90%) between migraine attacks than patients with common migraine (33%). These observations of abnormal platelet sensitivity causing or at least predisposing migraine, soundly base the use of aspirin or other antiplatelet approaches to migraine prophylaxis. The first of these studies was reported in The Lancet by O'Neill and Mann in 1978. This showed that prophylactic use of aspirin had a beneficial effect on many but not all migraine sufferers, reducing both the number and the severity of attacks. A subsequent study by D'Andrea and associates reported in Stroke in 1984 adds further support to the likely benefits of aspirin given prophylactically. They showed that administration of aspirin to patients with common and classic migraine who were shown to have in creased levels of beta thrombo-globulin and platelet factor IV both between and during attacks, resulted in significant reduction in levels of both. Similar observations have been made by other investigators.

In conclusion then, it would seem that there is reasonable evidence to base the suggestion that the association of migraine with diving is due to platelet over-reaction to decompression stress with or without bubble formation. It would also seem reasonable to assume that migraine sufferers may be at increased risk of DCS because of their haemostatic "over reactivity".

Although aspirin and similar antiplatelet drugs have not been shown to have a convincing benefit in protecting against DCS in humans, the use of aspirin in such an identified subgroup as migraine sufferers might be expected to show more benefit. Of course, such studies are not likely to be done.

PERSONAL VIEW

I was introduced to diving at Miner's Head, Great Barrier Island, New Zealand in 1972. My early diving experiences were unforgettable but made more so by the fact that almost without exception and even with very conservative, 30 feet scallop dives, I would suffer migraine. Other than with diving, I would normally have suffered no more than two migraine headaches a year. In 1976 I began taking aspirin in the form of Palaprin Forte, beginning 1-3 days before expected diving excursions. This has been completely effective in preventing post dive migraine headache. On occasions I have not taken aspirin and more often than not, I have developed a severe headache. However, in recent years I have become a less adventurous diver, preferring the lesser risks and discomfort of shorter and shallower dives.

REFERENCES

MIGRAINE

Anderson B et al. Migraine like Phenomena after Decompression from Hyperbaric Environment. Neurology 1965; 15: 1035-1040.

D'Andrea et al. Study of Platelet Activation in Migraine: Control by Low Doses of Aspirin. Stroke 1984; 13(2): 271.

Dhirendra S Bana. Headache from the Depths. Headache September 1980; 20(2): 230. Describes a delightful interview with a diver suffering related migraine manifesting at less than 30 feet before surfacing.

Engel GL et al. A Migraine-like Syndrome Complicating Decompression Sickness. War Med (Chic). 1944; 5: 304.

Hanington EV. Migraine, a Platelet Disorder. Lancet 1981; 2: 720.

Manoti C et al. Platelet Activation in Migraine. Thromb. Haemostasis (Stuttgart). 1983; 50(3): 758.

Martin KH and Nichols. Observation on Platelet Changes in Man after Simulated Diving. Aerospace Medicine 1972; 43: 827.

O'Neill and Mann. Aspirin Prophylaxis in Migraine. Lancet 1979; 2: 1179.

Violi et al. Beta Thrombo-globulin Plasma Levels in Common Migraine Thromb. Haemostasis (Stuttgart). 1984; 51(2): 295.

OTHER

Bennett & Elliott. The Physiology and Medicine of Diving. 1982, 3rd Edition.

Eckenhoff and Hughes. Haematologic and Haemostatic Changes with Repetitive Air Diving. Aviation, Space and Environmental Medicine July 1984; 55: 592.

Edmonds, Lowrie and Pennefather. Diving and Sub-Aquatic Medicine. Diving Medical Centre Publication, 1981.

Hickey, Donald B. Outline of Medical Standards for Divers. Undersea Biomedical Research. December 1984; 11(4): 407-432.

Lehtosalo et al. Bubbles & Blood Changes in Intercranial Veins. ACTA Neuro. Pathol. (Berlin) 1983; 59(2): 139.

Levin et al. Blood & Vessel Wall Changes in Decompressed Dogs. Journal of Applied Physiology May 1981; 50: 5944.

Makio Murayama. Ex-Vivo Platelet Aggregation Induced by Decompression. Thrombosis Research 1984; 33: 477.

O'Brodovich et al. Hypoxia Alters Blood Coagulation During Acute Decompression in Humans. J Applied Physiology 1984; 56(3): 666.

Philp RB. A Review of Blood Changes Associated with Compression-Decompression: Relationship to Decompression Sickness. Undersea Biomedical Research June 1974; 1(2): 117.

Popovic et al. L Dopa and Aspirin Free Treatment Beneficial in Experimental Decompression Sickness. Proceedings of the Society for Experimental Biology in Medicine 1982; 169, 140.

Problems of Altitude Decompression Sickness. Brit. Med. J. 1983; 286: 1498.

DIVING IN PREGNANCY

Bolton ME. Survey of 208 Women Diving in Pregnancy. Undersea Biomedical Research 1980; 7: 183.

Bolton et al. American Journal of O and G May 1983; 146: 48.

Gillman et al. Foetal Development in Hamsters. Aviation Space and Environmental Medicine November 1983; 54(11): 1040.

Newhall JS. Diving in Pregnancy - A Review. American Journal of O and G August 1983; 15(8): 140.

Turner B and Unsworth I. Intrauterine Bends. Lancet 1982; i: 905.

Dr JF Cleland's address is the Pathology Department, Green Lane Hospital, Auckland, New Zealand.

LETTERS TO THE EDITOR

Duke University Medical Center
Durham, North Carolina 27710

29 April 1986

Dear Sir

I have been recently appointed Chief Editor of the new Journal of Hyperbaric Medicine, published by the Undersea Medical Society, starting this year, 1986. This journal will enable medical practitioners, researchers, and other professionals in the field of hyperbaric medicine to keep abreast of current scientific research in this specific area. I am soliciting now for original contributions focusing on clinical application of hyperbaric oxygen (HBO), oxygen effects on body metabolism, treatment protocols, and protectants against oxygen toxicity.

In addition to original research and clinical communications, the journal will carry reviews, technical and preliminary notes, abstract of the literature, letters to the editors and book reviews.

I would be grateful if you would print this letter so that members of SPUMS who might be interested in submitting a contribution know where to send it.

Manuscripts should be submitted to:

Elaine C Frost
Managing Editor
Undersea Medical Society, Inc.
9650 Rockville Pike,
Bethesda, Maryland 20814
USA

Yours sincerely

Enrico M Camporesi, MD
Professor of Anesthesiology
Assistant Professor of Physiology
Director, Clinical Services
The Hyperbaric Medical Center

PROBLEMS WITH MEDICAL CERTIFICATES

Diver Instruction Services
12 Waratah Avenue
The Basin VIC 3154

7 April 1986

Dear Sir

I enclose copies of recent medical certificates supplied by students of our dive school. The names of all concerned have been omitted and the students have granted permission for publication.

I am concerned that many students are being passed, or should I say not being failed on a diving medical if their fitness is questionable. It appears to me that the decision about fitness to dive is therefore being passed to the instructor, and the student.

The Certificate for student A reads: "... has been examined by me for fitness for training in SCUBA diving .... is physically small and of light build. He is healthy and normal for his age and weight but he could expect to have problems in any but the most protected environment, or if he used equipment inappropriate to his size and strength. However, in a sheltered area with 'hand-holding' supervision, it could be possible to train him in underwater activities when he is completely well."

In this case, if the student is taught in a totally "protected environment", in "calm conditions", and a "hand-held situation", what is he going to learn? What happens once he completes training and is turned loose into a normal diving situation? When the student is "completely well" relates to his asthmatic condition!!!