A Review of Cerebral Damage as a Consequence of Exposure to Emboli

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EXECUTIVE SUMMARY

This study was conducted on behalf of the Offshore Safety Division (OSD) of the Health and Safety Executive (HSE). OSD have a responsibility to minimise risk and to protect the health of the working population in the offshore environment. This particular study focuses on the need to understand the potential long-term health implications of a career in commercial diving. It does not review the diving literature per se, but attempts to identify a relevant model from other areas of research which can be used to predict long-term health deficits as a consequence of exposure to emboli within the central nervous system (CNS).

Previous studies (Refs. 1, 2, 3, 4, 5, 6, 7) have identified sub-clinical symptoms of CNS damage in divers; this includes those divers who have a history of Decompression Illness (DCI) with an apparently successful therapy, and those who have no DCI history. It is believed that microemboli which are present during asymptomatic decompressions ('silent' bubbles) may be a causal factor in CNS deficits in divers. The sub-clinical symptoms identified include abnormal neurophysiological responses compared to age-matched subjects. However the significance of these findings for the long-term health of the individual diver is unclear. It was therefore decided to search the scientific and medical literature in order to determine whether models from other areas of research might provide further information relevant to OSD's concern about the potential long-term health implications of sub-clinical symptoms caused by microemboli.

High altitude flying and space flight were identified as relevant to the study, since aviators and astronauts are at risk of DCI due to reductions in ambient pressure at altitude. The initial objectives of the study were therefore to determine whether research in the field of aerospace medicine has identified any CNS deficits in aviators or astronauts, similar to those identified in divers, and to determine their potential for significant long-term health effects.

The aerospace medical literature was searched for information relating to decompression, gas emboli, neurological function and psychological impairment. A considerable body of literature was identified relating to symptomatic aviation DCI, but no reports of work on the potential long-term health effects of exposure to 'silent' bubbles during high altitude flight were identified by this study. Personal communication with aviation medicine experts appears to confirm that current aerospace research is directed towards the prevention of overt symptomatic DCI which may incapacitate the aircrew or astronauts during their mission.

In view of this finding, the study was extended to consider other potential models. Cardiac surgery was identified as having possible similarities with diving, based on the fact that gaseous and other emboli are introduced into the arterial circulation of the patient during cardiac surgery. The literature confirmed that emboli have been identified by ultrasound and retinal angiographic monitoring techniques in the CNS and cardiovascular circulation. Gaseous emboli are generated by surgical opening of the circulatory system, and by the use of oxygenators during cardiopulmonary bypass. Some emboli are also particulate in nature, consisting of fatty and platelet aggregates, sclerotic debris, and particles from materials used during surgery.

Neuropsychometric studies of cardiac patients before and after surgery have confirmed that some patients demonstrate an increased level of intellectual, cognitive and behavioural dysfunction after surgery. These consist of loss of memory, lapses of concentration, and
impairment in cognitive tests. In patients who have otherwise made a full clinical recovery, the dysfunction has been identified by psychometric tests. It is believed that such deficits are caused by damage to the CNS, resulting from occlusion of the circulation due to emboli, together with other ischaemic causes such as low blood pressure during the operation. There is strong evidence to demonstrate the proposed link between emboli during surgery and post-operative neuropsychological deterioration. Such deterioration is known to persist for at least five years after surgery in a small number of patients.

The current study presents the hypothesis that emboli identified during cardiac surgery are similar in effect to those formed in divers during a decompression, and that the subsequent CNS deficits are likewise similar in character. For the purposes of comparison with diving research, a preliminary attempt has been made to adopt a common, quantitative grading system for the classification of emboli during surgery and in diving. This grading system is based on a qualitative process for comparing the venous gas emboli (VGE) in the pulmonary artery of divers and arterial emboli in the brain of cardiac surgery patients. This comparison has enabled the study to explore the possibility of correlating observed CNS deficits in cardiac patients with emboli grades in divers, and of using cardiac surgery as a model by which to predict potential long-term health effects in divers.

The adoption of this grading system has identified that levels of emboli graded ‘High’ are present during coronary artery surgery procedures. This level of emboli is equivalent to a Doppler KM score of III or IV in divers. This grade of emboli is associated with at least a 30% incidence of neuropsychological dysfunction at two months post-surgery. It is noted that this may be an underestimate, and the actual incidence of deficit in patients may be as high as 50-60% at two months post-surgery. Such deficits are believed to persist for up to five years in a number of subjects, with one study indicating sub-clinical deficits in over 40% of subjects. When these results are cross-correlated to diving research, it indicates that there may be a greater than 30% incidence of sub-clinical deficit associated with Doppler KM grades III and IV. This predicted incidence of sub-clinical deficits is directly comparable with levels of deficit observed in a sequence of research studies in divers. Previous work has indicated that approximately 6% of operational offshore air dives may generate levels of gas graded Doppler KM III and IV.

The study concludes that the mechanism of damage in cardiac patients appears in many respects to be similar to that in divers, and the subsequent CNS deficits may be comparable in terms of presentation and degree of deficit. However while cardiac surgery may be a reasonable model for emboli in diving, there are insufficient data on long-term follow-up studies e.g. ten or twenty years after the original insult, to be able to use the model to predict the long-term quality of life for divers. Nevertheless these findings support OSD’s concern about the potential of asymptomatic ‘silent’ bubbles to cause subsequent CNS damage. The findings strongly support the view that the CNS deficits seen in divers are primarily due to the presence of emboli in the arterial circulation. It confirms the current direction of OSD diving research strategy, namely to endeavour to reduce levels of gas during a decompression; to investigate the occurrence of sub-clinical neurological deficits in divers by means of standard neuropsychometric tests and retinal angiography; and to correlate these results with diving exposure.
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1. INTRODUCTION

1.1 OBJECTIVES

The original objectives of this study were to:

- determine whether research in the field of aerospace medicine has identified any long term health effects, similar to those implicated in diving, in aviators or astronauts.

- if so, to determine the potential causal mechanisms identified by the research and determine whether these may be relevant to the diving environment.

These objectives were subsequently extended to:

- determine whether the generation of emboli in patients during cardiac surgery may act as a model for emboli in divers.

- determine whether there is evidence of long-term central nervous system (CNS) deficits in cardiac surgery patients which may be attributable to emboli during surgery.

- to use the cardiac surgery model to assess the potential for long-term health deficits in divers.

1.2 BACKGROUND

The sponsor for the work was the Offshore Safety Division (OSD) of the Health and Safety Executive (HSE). OSD has a responsibility to protect the health, safety and welfare of offshore workers. This review is presented in response to OSD’s concern about the probable acute and long-term adverse health effects arising from a career in diving, which are reported elsewhere. The significance of the reported health effects are not yet fully understood. These health effects primarily affect the central nervous system, lung function and the long bones, and are reported elsewhere. Most clinical deficits which have been observed are the result of inadequate decompression, which has resulted in Decompression Illness (DCI) and subsequent health deficit. However sub-clinical deficits have also been identified in divers who have not experienced DCI (Refs. 1, 2, 3, 4, 5, 6, 7).

The current hypothesis is that such sub-clinical deficits may be attributable to microbubbles and emboli which enter the arterial circulation during decompression and subsequently cause ischaemic or mechanical damage to the CNS. An alternative mechanism may be exposure to high levels of oxygen. However much further work is required to determine the extent and significance of these deficits, and to identify causal mechanisms.

Epidemiological studies may contribute to an improved understanding of the nature of long-term health effects in divers, but studies of this nature take several years to present results. There is therefore a need to identify a model which may be used to predict the possible long-term health effects of a career in diving, and to enhance understanding of causal effects.

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1 The term ‘Decompression Illness’ has been adopted in this paper to include both decompression sickness and arterial gas embolism.
To this end, this study was initiated to review the aerospace literature, given that there are potential similarities between divers and aircrew and astronauts. Both groups experience decompression and are exposed to high levels of oxygen for extensive periods. The objective of this study was therefore to determine whether any research conducted by the aerospace medical community on long term health effects may be relevant to diving.

In the course of the work it became apparent that one further field of study merited investigation. This was cardiac heart surgery involving bypass of the heart and of the lungs. Cardiac patients who undergo surgical intervention are exposed to the risk of gas emboli and other debris entering the arterial blood stream during extracorporeal oxygenation and filtration of the blood, and from the surgical intervention in the circulatory system. There is concern in the medical literature that such emboli may result in neurological and psychological dysfunction, which may affect the future quality of life of the patient. Because of the apparent potential similarities to diving of both the causal mechanisms and the resulting deficits, it was decided to include the cardiac surgery literature in this review.

1.3 REPORT STRUCTURE

This report presents the methodology adopted for the work in Section 2. The results of the literature search, firstly of the aerospace literature, and secondly of cardiac studies, are presented in Section 3. The data presented in Section 3 have been analysed and correlated with data reported in diving studies, and the results of this analysis are presented in Section 4, Analysis. Discussion and Conclusions complete the main body of the report, although readers may wish to refer to the subsequent Glossary and Appendices.
2. METHODOLOGY

2.1 DATABASE AND LITERATURE SEARCH

The Scope of Work for the study provided for the use of on-line database facilities to identify any openly published literature on long term health effects amongst aircrew and astronauts. The databases selected for search were:

- National Aeronautics and Space Administration (NASA)
- National Technical Information Service (NTIS), US Department of Commerce
- MEDLINE (world-wide medical database)
- Embase (European medical database)

It was considered by accessing the NTIS database, which holds research results from US Government work, that this would identify any work sponsored by the US Air Force or Navy into the long term health status of aircrew, associated with decompression.

Previous copies of the journal, 'Aviation, Space and Environmental Medicine' for the period 1988 to 1996 were searched for relevant articles.

2.1.1 Keywords

The keywords combined in various combinations for the database search were:

- Aircrew or astronaut
- Aseptic bone necrosis
- Bubbles
- Cardiovascular
- Cognitive
- Decompression
- Diver
- Emboli
- Epidemiology
- Gas
- Hyperbaric
- Hyperbaric oxygen treatment
- Hyperoxia
- Long term health
- Neurological deficit
- Neurological impairment
- Nervous system deficit
- Pilmanis
- Psychometry
- Psychological impairment
- Surgery
- Transplant

2.2 PERSONAL COMMUNICATION

During the course of the study, contact was made with DERA Farnborough, Centre for Human Sciences, to discuss current concerns within the field of aviation decompression. Contact was also made with the Institute for Environmental Medicine, University of Pennsylvania, which undertakes work on aviation and diving decompression and is also a centre of expertise on oxygen toxicity. The Wolfson Institute, University of Dundee, was contacted for assistance with the identification of references on the neurological sequelae of cardiac surgery.
3. RESULTS

3.1 AVIATION AND SPACE MEDICINE LITERATURE

The following sub-sections outline the findings of the literature search, based on the keywords identified in Section 2.1.1, the review of 'Aviation, Space and Environmental Medicine', and discussions with aviation medicine specialists.

3.1.1 US Aviation And Space Medicine Research

Several hundred titles were identified by database search and review of the literature. These various reports confirmed that aviators and astronauts are exposed to reductions in ambient pressure during ascent to altitude and while remaining at altitude. This reduction in pressure may provoke clinical DCI. The mechanism is understood to be the separation of nitrogen gas from solution, in a similar manner to that experienced by divers, and thus confirms the apparent suitability of aerospace decompression as a model for diving.

The reports identified by the literature search included a range of US Air Force reports relating to specific health issues among aviators. However few reports were directly relevant to the long term health implications of decompression, arterial emboli, hypoxia or hypoxia. The many papers on the neurological symptoms of, and treatment for, aviation DCI, where clinical symptoms were observed, have been excluded from the main part of this review (short extracts are included at Appendix 1 to indicate the main focus of current aviation decompression research). The reason for their exclusion is that the main objective of this study is to focus on the potential long-term and sub-clinical health effects of emboli, rather than the prevention of clinical DCI per se.

Review of the literature indicates that the main focus of past and current work in aviation and space medicine is the prevention of clinical DCI, in order that aircraft and space missions are not prejudiced. Confirmation that US government research is primarily limited to the prevention of DCI is found in Dixon (Ref. 8), Kumar (Refs. 9, 10), Bason and Yacavone (Ref. 11), Webb (Ref. 12) and Webb and Pilmanis (Ref. 13). Dixon indicates that "the lack of understanding of long-term bubble effects" suggests that a reasonable approach to eliminating the risk of DCI under all conditions is to increase the exposure pressure to prevent detectable bubbling. This is the only reported reference identified by this study to the possibility of long term effects. Kumar describes ground-based trials conducted by NASA in order to examine the risk of DCI at specific space suit pressures, and to formulate measures to reduce this risk. In doing so, the objective is to reduce the potential for the astronauts' performance to be impaired (to the extent of inability to perform complex tasks during extravehicular activity (EVA), or to compromise the entire mission). Bason expresses concern about the risk of acute DCI during chamber flights to train aircrew to recognise and deal with the effects of hypoxia. Webb indicates that current US research is directed towards the prevention of decompression illness in current and future fighter aircraft (Ref. 12) and for extravehicular activity during space flight (Ref. 13).

Personal contact with the Institute for Environmental Medicine, University of Pennsylvania, did not identify any further information within the U.S. research community into the potential long term health implications of exposure to microbubbles arising during an asymptomatic decompression in aviators or astronauts.
3.1.2 UK Aviation Decompression Research

Contact with DERA Farnborough confirmed the initial findings of the literature search, that any existing work on the long-term health consequences of 'silent' bubbles appears not to have been reported in the open literature. Current UK research is directed towards the definition of 'acceptable risk' flying protocols, which maximise the time at which an aviator can remain at high altitude and reduced ambient pressure, before clinical symptoms of DCI develop. The use of a low-pressure chamber enables DERA to simulate, and determine the risk of, a range of flying profiles. Risk is assessed by the number of bubbles generated in the venous system of volunteer subjects, with ultrasound scanning being used to monitor gas generation.

3.1.3 Conclusions From Review Of Aerospace Literature

It has long been known that the mechanism of aerospace decompression is similar in nature to diving, with the initiating event being a reduction in ambient pressure which results in the release of inert gas from solution in the body. Both the diving and the aerospace community have identified that there may be potential long-term health effects of microbubbles forming in the body during an otherwise asymptomatic decompression. However the published reports from aerospace medicine contribute little new information to existing understanding of long-term health issues relating to diving decompression and CNS arterial emboli. This apparent lack of data on the long-term health consequences of 'silent' bubbles in aviators and astronauts means that for the purposes of this study, it is not possible to use this population as a model for divers.

The few papers of limited relevance to long-term health issues are summarised in Appendix 1.

3.2 CARDIAC SURGERY LITERATURE

The search of the cardiac literature was successful in identifying a number of papers which analysed the prevalence and neurological effects of microemboli during various cardiac procedures. These papers are summarised below, and the results relevant to the objectives of this study are analysed in Section 4.

3.3 DAMAGING MECHANISMS

Sub-clinical brain injury is associated with cardiac operations, including coronary artery bypass grafts (CABG) (Refs. 14, 15) and 'open heart' valve operations (Ref. 16). Both procedures require temporary artificial maintenance of the blood’s circulation and oxygenation with cardiopulmonary bypass. The two most serious complications of cardiopulmonary bypass (CPB) are identified as diffuse general disorder (encephalopathy) from global cerebral anoxia and localised cerebral dead tissue caused by loss of blood supply. Patients may also suffer more subtle neuropsychological deficits after cardiopulmonary bypass, probably from patchy ischaemia in the cerebral arteries.

Damaging mechanisms are believed to include macroembolism from blood clots in the left ventricle, debris from aortas on clamping, valve debris or air (Ref. 14), the presence of platelet and leucocyte aggregates and fibrin in donated blood (Ref. 15); microemboli in low mean arterial blood pressure during surgery (Ref. 17), and gas emboli. Variables which may affect the presence of gas emboli include oxygen gas flows in bubble oxygenators, air leaking
around improperly secured cannulae, and inadequate defarking of the heart during openheart procedures. Multiple small areas of ischaemia may arise from microemboli of gas, fat, aggregates of red cells, platelets, or fibrin and particulate debris from silicone antifoam and plastic tubing. Also, global hypofusion may occur from low arterial pressure, reduced cerebral blood flow, and the non-pulsatile blood flow of most bypass systems. Although occurring by these various different mechanisms, the end result of this brain insult is ischaemic injury. Operative risk factors appear to include open heart procedures, severity of pre-existing disease, duration of low arterial blood pressure, blood loss, oxygenator failure, duration of bypass time (Ref. 18), type of oxygenator used and inadequate filtration of the blood (Refs. 19, 20, 21).

3.3.1 Emboli Detected By Retinal Angiography

The presence of emboli in the arterial circulation have been confirmed by the use of retinal angiography during and after surgery. In Shaw's study (Ref. 22) examination of the ocular fundi of patients demonstrated localised loss of blood flow to the retina, indicating the presence of microemboli. Blauth (Ref. 20, 23, 24) adopted retinal fluorescein angiography to identify microemboli in the retinal circulation and associated microvascular occlusions and endothelial defects present during surgery. In a study of cardiac patients (Ref. 23) he identified the presence of microemboli in all patients (n=21) during bypass, ranging between 5 and 16 microembolic events. Eleven of the 21 patients had delayed drainage of dye, and 4 had focal leakage of fluorescein. He records that there was a mean of 3.5 (range 1 to 7) blocked arterioles of less than 50μm calibre and a mean of 6.3 (range 1 to 10) focal areas of capillary non-perfusion per 30 degree field of retina centred on the macula per patient during the bypass procedure. Repeat studies 30 minutes after bypass showed partial reperfusion with occlusions in 4 of the 5 patients and a decrease in mean microembolic count from 12.6 to 4.8. At a median of 8 days (range 5 to 11) after surgery, 2 of 16 patients had persistently occluded retinal vessels.

In a second study by Blauth of patients undergoing coronary artery surgery (Ref. 19), the objective was to assess the relative effectiveness of bubble and membrane oxygenators during cardiopulmonary bypass in filtering out emboli in the extracorporeal circulation, which might otherwise cause CNS damage. Blauth proposed that because of the common blood supply between the eye and the brain, changes in the retinal circulation would match those in the brain. He identified the mean overall area of retinal non-perfusion per retina in the group of patients whose bypass had been achieved using a bubble oxygenator as 0.29 mm² (range 0.04-1.23 mm²). This compares to a mean of 0.05 mm² (range 0-0.49mm², n=17) in the group of patients where a membrane oxygenator had been used. It is also noted that in those retinas with occlusions, the mean resultant area of non-perfusion was less in the membrane oxygenator group (0.11mm²; n=8) than in the bubble oxygenator group (0.29mm²). It was not possible to differentiate between fluorescein leaks caused by air bubbles or by platelet aggregate damage.

In a later 1990 study (Ref. 20), Blauth compared the median areas of retinal ischaemia during cardiopulmonary bypass of patients on a bubble oxygenator against those where a membrane oxygenator had been used. In the bubble oxygenator group the total area of retinal ischaemia was a median of 0.22mm², (range 0.21 to 0.27mm²). In the membrane group, the median total retinal ischaemia was 0mm² (range 0 to 0.16mm²).

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3.3.2 Emboli Detected By Ultrasound

Transcutaneous Doppler ultrasound during cardiopulmonary bypass and other operations involving the arterial circulation has also been used to confirm the presence of cerebral emboli (Refs. 21, 25, 26, 27).

Spencer (Ref. 26) used transcranial Doppler ultrasound to detect emboli in 91 patients undergoing carotid endarterectomy. Both air bubble emboli and formed-emboli (i.e. non-gaseous particulate) were detected, with 38% of patients having air bubbles. Air bubble emboli were not associated with clinical symptoms, whereas in extreme cases non-gaseous emboli which were present for several hours were associated with stroke. It is relevant to note that Spencer appears to be the only researcher active in the diving research community who has also made a contribution to the debate in the cardiac surgery literature about the presence and significance of emboli. He comments that the qualities of the bubble in cardiac surgery are similar to those of decompression.

Pugsley (Refs. 21, 28) investigated the efficiency of filtration in reducing the number of embolic events during surgery and related this to neurological/neuropsychometric status at two months after surgery (see section 3.4 below). He identified that emboli were apparent in all bypass patients during surgery. In one study he counted the number of ‘microembolic events’ (MEE) during a 30 minute period of the surgical procedure. An MEE was defined as a high amplitude signal detected by Doppler, which was more than twice the maximum amplitude observed under steady flow conditions. Where the surgeon adopted additional filtration of the blood, such patients had between 1 and 10 ‘events’, compared to between 30 and over 700 ‘events’ in a group of non-filtered patients undergoing the same surgical procedure (Table 1).

<table>
<thead>
<tr>
<th>Time of monitoring</th>
<th>Filtered patients (n=20)</th>
<th>Non Filtered patients (n=20)</th>
<th>Significance (Wilcoxon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During CPB Median (MEE/30 min)</td>
<td>6</td>
<td>243</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>0-10</td>
<td>30-768</td>
<td></td>
</tr>
</tbody>
</table>

In a second study Pugsley identified high intensity transcranial signals (HITS) in 94 patients undergoing coronary artery surgery with and without additional filtration of the extracorporeal circulation. These patients were monitored by Doppler to detect and record emboli in the cerebral circulation (Table 2) (Ref. 21). The mean period of observation was 100 minutes, i.e. the mean duration of the bypass procedure. Patients’ postoperative performance was subsequently measured using a neuropsychological test battery (see section 3.4 below).
Table 2
High intensity transcranial signal count (HITS) during cardiopulmonary bypass (CPB) (Ref. 21)

<table>
<thead>
<tr>
<th>HITS Count Total over 100 Minute Period</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200</td>
<td>58</td>
</tr>
<tr>
<td>201-500</td>
<td>13</td>
</tr>
<tr>
<td>501-1000</td>
<td>16</td>
</tr>
<tr>
<td>≥ 1000</td>
<td>7</td>
</tr>
</tbody>
</table>

Harrison (Ref. 27) reports on the same study and notes that during bypass, filtered patients had a median of 6 high amplitude signals per 30 minute period (range 0-10). Non-filtered patients had a mean of 243 (range 30-768).

Tingleff (Ref. 16) used intraoperative transthoracic echoangiography (ITEE) to monitor two groups of patients undergoing heart operations. Group 1 consisted of 15 patients undergoing 'open heart' aortic or mitral valve operations, while Group 2 consisted of 15 patients undergoing coronary arterial bypass grafting (CABG) i.e. not involving surgical opening of the interior of the heart. The objective of the study was to determine the relative risks of 'open' and 'closed' heart surgery with a view to identifying periods of risk and localising the sources of air. The grading system adopted was grade 0 = no air; grade 1 = air that did not dominate the echocardiogram; grade 2 = air that dominated the echocardiogram. Echocardiogram monitoring was conducted during and after cessation of cardiopulmonary bypass. The results are given in Table 3.

Table 3
Detection of air emboli by intraoperative transthoracic echoangiogram (Ref. 16)

<table>
<thead>
<tr>
<th>Group</th>
<th>Echocardiogram Grade (All recorded during bypass phase of the operation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Group 1 (open heart) (n=15)</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 (coronary artery bypass grafting) (n=15)</td>
<td>7</td>
</tr>
</tbody>
</table>

It is observed by Tingleff that normal clinical postoperative observation did not reveal any neurologic deficits in any of the patients in either Group 1 or 2. No psychometric or neurophysiological tests are reported.

Oka (Ref. 29) used transthoracic echoangiography to monitor emboli in two groups of patients undergoing cardiac surgery. The first group underwent 'open heart' cardiectomy with cardiopulmonary bypass, while the second group underwent 'closed' coronary artery
bypass grafting (CABG). The presence of emboli immediately after bypass were graded on a scale 0 to III (see footnote 2). The results are presented in Table 4.

Table 4
Differences of air embolism detection in open cardiotomy and coronary artery bypass graft (CABG) groups (Ref. 29)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Open Cardiotomy (n=15)</th>
<th>CABG (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>

Seventy-three percent of the ‘open heart’ surgery group presented with emboli, compared with only 11% of the CABG group. The difference was statistically significant (P<0.005). Both groups were assessed for central nervous system effects after the operation (see section 3.4 below).

3.3.3 Conclusion

From the data presented above, it appears that different cardiac procedures are associated with varying levels of emboli, as detected by ultrasound and retinal angiographic techniques. Risk factors appear to include ‘open heart’ as opposed to ‘closed heart’ procedures, use of bubble rather than membrane oxygenators, and the absence of additional filtration of the arterial circulation during bypass. However the majority of cardiac operations appear to generate emboli in some form in most patients.

3.4 EVIDENCE OF CEREBRAL DYSFUNCTION

3.4.1 General Reviews

Utley (Ref. 25) identifies that the observed incidence of brain dysfunction following cardiopulmonary bypass depends upon the sensitivity of the test or indicator used. Deterioration in psychomotor tests (nature unspecified) is quoted in 10-15% of patients, although the functional results of these changes in test performance are not deemed to be discernible in most patients.

In a general review, Campbell (Ref. 18) reports that a small percentage of patients exhibit residual, but minor, neurological deficits for up to one year after bypass surgery. Neuropsychological impairment is noticed most often on tests of new learning ability, auditory short-term memory, psychomotor speed, attention and concentration. Behavioural changes include confusion and disorientation, resolving after two weeks. Cognitive impairment is reported as transient, resolving within two to three months.

2 0 = no air emboli. I = trace to moderate contrast air emboli lasts within 30 heart beats, seen less than 3 times during observation. II = Moderate contrast air emboli lasts more than 30 heart beats, seen 3 or more times during observation. III = Dense contrast air emboli lasts more than 30 heart beats, seen more than 3 times during observation.
Memory deficits appear to be more persistent, detected at up to two years post-operation. She surmises that, depending on the patient's age, preoperative level of functioning and level of job responsibility, the 'subtle' neuropsychological changes identified in the literature could interfere with the patients' lifestyle.

3.4.2 Neurological Examination

In an early study, Javid (Ref. 17) conducted neurological examinations of 81 patients following cardiac surgery involving cardiopulmonary bypass. Forty-one patients are noted as having neurological signs after surgery, including nystagmus, double vision, and paresis. Thirty-five had disordered behaviour and intellectual deficit. Twelve patients had persistent signs of intellectual impairment and neurological dysfunction after discharge from hospital. Seventy-eight patients were followed up after two years, when 3 continued to show some mild deficits.

3.4.3 Combined Neurological And Neuropsychometric Studies

Sotaniemi (Ref. 30, 31)

Sotaniemi conducted a one-year follow-up of 100 patients who underwent open heart operations for valve replacement. A clinical neurological examination was undertaken at 2 and 5 days before surgery, and at 10 days, 2, 6, 9 and 12 months after surgery. EEG and neuropsychological tests were also performed. Thirty-seven patients had neurological abnormalities at 10 days post-surgery (paresis, motor and sensory impairment). At the end of monitoring (8 months to 1 year), 7 patients had neurological disability (hemiparesis, intellectual impairment, motor defects). Deficits correlated with perfusion time (deficits were present in 50% of patients with perfusion longer than 2 hours), with problems with the oxygenator, and in three cases with embolism.

In a follow-up study of 44 patients who had undergone open-heart valve replacement surgery, Sotaniemi conducted neurological and neuropsychological examinations of patients five years after surgery (Ref. 32). All the operations had been conducted using a bubble oxygenator and the application of moderate hypothermia. Clinical neurological examination and neuropsychological tests were conducted pre-operatively, and at two months, one year and five years post-operatively. The neuropsychological tests battery consisted of seven sub-tests of mental flexibility, verbal memory proficiency, psychomotor speed, planning ability and frontal lobe functions, symmetry, recognition, attention and audio-verbal memory. The post-operative score for each sub-test, and the sum score of the seven sub-tests (NP-Index), was compared with the pre-operative values for each individual, and with group means.

At five years, ten patients reported some degree of memory impairment, although this was considered unimportant in daily activities. Of these patients, seven had previously displayed some clinical neurological dysfunction ten days after surgery, and had also demonstrated impairment in the first neuropsychological set of tests at two months after surgery. Five years after surgery three patients still displayed residual motor hemisindrome attributable to operative complications (which are not defined by Sotaniemi). Two further patients showed renewed signs of slight unilateral hyperreflexia, similar to symptoms which they had experienced after the operation, but which had resolved with time. A group of patients (n=21) who had displayed some neurological dysfunction ten days after the operation (motor or sensorymotor abnormalities) displayed a statistically significant decline in performance at the five year follow-up on those aspects of the neuropsychological test.
battery which examined frontal lobe ability, learning and recognition. Patients who had not displayed any neurological signs after surgery performed better on the test battery than their pre-operative score. The duration of extracorporeal circulation in the operation was one of the main determinants of the long-term neuropsychological outcome. This would seem to be due to the positive correlation between perfusion time and clinical complications during the operation. It was observed that a long duration of perfusion impaired the overall neuropsychological performance, independent of the clinical neurological outcome immediately after the operation. It was also observed that the difference in test battery performance between groups of patients who had experienced short (<2 hours) and long (>2 hours) perfusion was accentuated during the follow-up time.

Pugsley (Ref. 28)
Pugsley undertook a clinical neurological examination of coronary artery surgery patients who had undergone cardiopulmonary bypass (CPB), with and without additional filtration (n=40). Patients were randomly assigned to the filtered or non-filtered groups and were subsequently assessed for new 'soft' neurological signs such as drowsiness, incoordination, and nystagmus, and localised specific (focal) dysfunctions e.g. muscular weakness and visual field defects. Assessments were conducted at 1 day, 8 days and 8 weeks after surgery. In addition the same patients undertook a neuropsychological battery of ten tests of memory, visual motor skills, reaction time, attention span, intelligence and mood state. The results of the neurological examination are presented in Table 5.

Table 5
Neurological dysfunction following coronary artery surgery
(Ref. 28)

<table>
<thead>
<tr>
<th>Neurological Signs</th>
<th>Filtered CPB (n=20)</th>
<th>Non-Filtered CPB (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal neurology</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>'Soft' signs of dysfunction</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

As reported in 3.3.2 above, filtered bypass patients had fewer bubbles than non-filtered patients. It is apparent that the non-filtered group had a higher incidence of dysfunction (35%) than the filtered group (15%). Verbal memory deficit was identified by the neuropsychological test battery performance at 8 weeks in 12 of the total of 40 patients; Pugsley comments that filtered patients performed better on this test than the non-filtered group, implying that there is an association between quantities of emboli and subsequent CNS dysfunction.

Pugsley (Ref. 21)
In a later study by Pugsley a total of 100 patients were randomly allocated to two groups, one with filtered CPB and the other with non-filtered CPB. In both cases a bubble oxygenator was used and the procedure involved coronary artery surgery. Patients were assessed by standard clinical neurological examination pre-operatively, at 1 and 8 days and at 8 weeks after surgery. Their neuropsychological performance was evaluated by means of a battery of 10 tests of memory, visual motor skills, reaction time, and attention. A deficit in performance in a single test was defined as a drop of 1 standard deviation (based on the group per-surgery mean) when comparing the individual’s pre and post-operative scores. A deficit in the individual’s overall performance was classed as significant if they demonstrated a deficit in two or more of the ten tests.
No patient in either the filtered or the non-filtered group had focal neurological signs at one day, 8 days, or 8 weeks after surgery. However neuropsychological deficits were apparent when test results were analysed (Table 6).

<table>
<thead>
<tr>
<th>Test Result</th>
<th>8 Days</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Filtered (n=26)</td>
<td>Non-Filtered (n=31)</td>
</tr>
<tr>
<td>No change (0-1 tests showing deficit)</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Deficit (deficit in &gt;1 test)</td>
<td>12</td>
<td>22</td>
</tr>
</tbody>
</table>

At 8 days, 96.5% of all test subjects showed some small deterioration in performance, but it is noted that at this stage post-operatively, performance on the neuropsychological battery is affected by factors such as tiredness and the effects of analgesics (P<0.05). Due to fatigue, some of the subjects failed to complete the tests satisfactorily, while others of the test population were discharged early from hospital. Test results from all of these patients have been excluded from the numbers in Table 6. At 8 weeks, 94.6% of test subjects still showed some small deterioration, although this observation should be qualified by noting that the population numbers varied at each stage of testing. Deficits in performance (Table 6) occurred in 8% of the filtered patients, and 27% of the non-filtered patients (P<0.03). It is noted as statistically significant that the filtered patients showed less deterioration than the non-filtered patients on 8 of the 10 tests (P<0.05, binomial).

All 94 patients who completed the neuropsychological assessment at 8 weeks had good quality transcranial Doppler recordings taken during surgery. Pugsley compared the neuropsychological deficits identified in patients with the high intensity transcranial signal count (HITS), expressed as a total for the whole of the patients' bypass time. These data are presented in Table 7. It would appear that a high HITS count is associated with a higher incidence of neuropsychological deficit. Pugsley does not attempt to present Doppler scores by filtered or non-filtered groupings, although it is noted as significant that of the 16 patients who had neuropsychological deficits at 8 weeks, 4 were in the filtered group and 12 non-filtered.
Table 7
Neuropsychological deficit related to high-intensity transcranial signal (HITS) count during cardiopulmonary bypass (CPB)
(Ref. 21)

<table>
<thead>
<tr>
<th>HITS Count During CPB (Mean duration of 100 minutes)</th>
<th>No. of Patients</th>
<th>No. With Deficit</th>
<th>% with Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 200</td>
<td>58</td>
<td>5</td>
<td>8.6</td>
</tr>
<tr>
<td>201-500</td>
<td>13</td>
<td>3</td>
<td>23.1</td>
</tr>
<tr>
<td>501-1000</td>
<td>16</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>≥ 1000</td>
<td>7</td>
<td>3</td>
<td>43</td>
</tr>
</tbody>
</table>

Oka (Ref. 29)
Oka examined patients following 'open heart' and CABG cardiac surgery for new neurological signs (Table 4). Three patients in a group of 15 'open heart' patients demonstrated postoperative CNS complications (cerebrovascular accident, prolonged disorientation). Of these patients, one had been assessed as having an echogram score of I, one as II, and one as III. Two patients in the CABG group had positive air emboli echograms (both Grade II) but had no post-operative complications.

Blauth (Ref. 23)
Blauth observed microembolic events during cardiopulmonary bypass by means of retinal fluorescein angiograms, and subsequently assessed the neurological and neuropsychometric status of the patients by means of a clinical examination and a set of four psychometric tests of memory, perceptual analysis and other functions. These examinations were conducted at a median of 9 days after surgery. The pre-operative angiograms were normal for all 21 patients; during bypass all patients had microvascular occlusions. After surgery transient neurologic signs developed in 3 patients; 2 had 'soft' signs of memory impairment and these patients also showed deficits in psychometry. One of these patients had an above average number of microembolic events, as recorded by angiograms. Twenty patients completed the set of four psychometric tests. At a median of 9 days post-operation, 13 (65%) had scores comparable with their pre-operative performance; 7 had at least one deficit greater than one standard deviation from the pre-operation group mean in at least one test. The mean total microembolic count for patients with a psychometric deficit was 11.1. occlusions per field, compared to a mean of 8.3 occlusions per field for patients with no deficit. This study would appear to identify some correlation between microemboli in the CNS circulation with subsequent neuropsychological deficit.

Blauth (Ref. 19)
In a further study Blauth examined the relationship between microembolic events identified by retinal angiography and neuropsychological deficit in patients where bubble and membrane oxygenators had been used during surgery. In a battery of 10 psychometric tests, a significant deficit was defined as a reduction in the individuals' post-operation score by more than one standard deviation of the mean score of the whole group. All 23 patients in the bubble oxygenator group had retinal occlusions during surgery, compared with 8 out of 17 (47%) for the membrane oxygenator group. A total of 22 patients in the bubble oxygenator group were assessed on the psychometric test battery at 8 days after surgery. Five had no measurable impairment. The mean number of tests with reduced scores per patient was 1.24 (range 0–5). In the membrane oxygenator group, data is available for 12
patients. Four of the 12 had no measurable impairment, and the overall mean number of tests with reduced scores per patient was 0.91 (range 0–2). The author notes that the difference between the two groups was not statistically significant, but comments that there appears to be a trend of less impairment after membrane oxygenation, where fewer emboli are observed.

**Smith (Ref. 32)**

Smith conducted a controlled prospective study, including neurological and neuropsychological assessments, psychiatric evaluation, measurement of cerebral blood flow, and visualisation of the cerebral vasculature by angiography, in a series of patients undergoing coronary-artery bypass surgery (CABS). The objective was to attempt to identify the mechanisms which may give rise to neurological complications after coronary artery bypass surgery. It was uncertain whether observed cerebral deficits could be due to the effects of cardiopulmonary bypass, cardiac surgery itself, or the general effects of major surgery caused by anaesthesia, analgesics and major disturbances of metabolism. A control group was therefore selected who had major thoracic or vascular operations, but not involving cardiopulmonary bypass or cardiac surgery. Examinations were conducted preoperatively, 8 days and 8 weeks postoperatively. In addition the neurological examination was carried out at 24 hours after the operation. The neuropsychological examination included the vocabulary and picture-completion subtests of the Wechsler adult intelligence scale to estimate intellectual level. Other tests included the Rey auditory verbal learning test (verbal memory); the Wechsler block design test (visuospatial ability); the Purdue pegboard test (visuomotoric skills); the trail-making test (A&B); a letter cancellation test; a symbol digit replacement test; and a two-choice reaction time test to assess attention and concentration. A drop of 1 standard deviation in the individual's performance between pre and post-surgery scores was considered significant. A drop in 4 or more test scores (out of 10) was considered 'severe', 2 or 3 as 'moderate', and 1 or less as 'no deficit'. The results of the clinical examination and the numbers of patients with signs of neurological dysfunction before and after surgery are presented in Table 8.

**Table 8**

**Number of patients with clinical neurological signs**

(Ref. 32)

<table>
<thead>
<tr>
<th>Time of Examination</th>
<th>CABS (n=53)</th>
<th>Control (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operation</td>
<td>9 (17%)</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>24 hours post-surgery</td>
<td>34 (64%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>8 days post-surgery</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>8 weeks post-surgery</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

One CABS patient had a motor defect still detectable at 8 days, and no patients had motor defects at 8 weeks, although one had a persisting visual-field deficit. There was no detectable neurological difference between the groups. In the neuropsychological tests at 8 weeks no CABS patient had a severe deficit, compared to three in the control group. About one third of both groups had persisting moderate deficits. In the CABS group at 8 days, 23 of the 30 patients with a diffuse pattern of neurological abnormality also had a neuropsychological deficit. One in three CABS patients had residual neuropsychological impairment at 2 months. The study suggested that these persistent neuropsychological deficits were likely to be due to the cardiopulmonary bypass, but could not explain the presence of similar deficits in the control group.
Newman (Refs. 33, 34)
In follow-up studies at twelve months by the same team 35% of CABS patients are reported to have had persisting neuropsychological deficits. Twenty-eight percent of other patients in the CABS group reported memory loss, 18% had difficulty in problem solving, 16% reported losses of concentration and an increased propensity towards mistakes. No data are presented at twelve months for control groups.

Shaw (Refs. 35, 36, 37, 38, 39)
Shaw reports on the outcome of a major prospective study of 259 coronary artery bypass surgery patients at up to six months post-operatively. Test techniques included neurological examination and psychometric assessment, using a battery of 10 standard tests of intellectual function (the Halstead Reitan trail-making test Part B; all seven subtests from the Wechsler memory scale; and the block Design and Vocabulary subtests from the Wechsler adult intelligence scale). Analysis of the test scores for individual patients showed that 147 (57%) showed a deterioration on at least one test score at six months (deterioration is assessed as performance more than one standard deviation below the pre-surgery score for the individual). The degree of impairment was usually classed as mild, and consisted primarily of impairment of attention span, calculation ability and audioverbal immediate memory. Eighty-one of these patients showed consistent deterioration in the same test scores at seven days and six months. One hundred and thirty of these 147 patients showed mild cognitive dysfunction at 6 months (score deterioration in 1 or 2 tests). Fifteen patients had moderate impairment at 6 months (score deterioration on 3 or 4 tests). Two patients were classed as having severe dysfunction (score deterioration in 5 or more tests). Seventy-one percent of patients had no significant symptoms, and 27% had minor symptoms, as reported by the patient. These included complaints of forgetfulness, mental slowness, or a reduced ability to concentrate. In functional terms, the impairment is reported as 'not often mattering to the patient'. However four patients were unable to return to work due to neurological symptoms, while one patient is reported as being prevented from returning to work because of intellectual impairment.

An analysis of predisposing factors by Shaw (Ref. 39) identifies that patients with a large drop in haemoglobin levels during surgery may be at risk of the development of retinal ischaemic lesions. Patients with atherosclerotic vascular disease were at risk of the development of retinal emboli. A history of cerebrovascular accident, transient ischaemic attacks, or vascular disease, and decreases in haemoglobin levels during surgery correlated with the more severe degrees of neuropsychological impairment. The study did not attempt to identify or quantify the presence of either fat or gas emboli during surgery, although it is noted that pre-existing disease may increase the risk of embolisation of cerebral vessels by dislodging particles during clamping.

Treasure (Ref. 40)
Treasure reports on the results of clinical neurological examinations, neuropsychological testing and blood flow measurements (intravenous injection of Xenon-133) in two groups of patients. The range of neuropsychological tests selected included vocabulary and picture completion tests of the Wechsler Adult Intelligence Scale, to test intellectual level pre-operatively, and the following battery of tests sensitive to diffuse cortical damage but resistant to practice effects: (1) the auditory verbal learning test to assess verbal memory, (2) the Wechsler Block Design Test to assess visuospatial ability, (3) The Trail Making Test to assess concentration and tracking, (4) the Purdue Peg Board Test for visual–manual coordination, (5) Symbol Digit Replacement Test, (6) Letter Cancellation, each testing both
attention and concentration, (7) a recognition test of non-verbal memory, (8) two choice reaction time tests.

Seventy six patients were undergoing coronary artery bypass surgery (CABS) involving cardiopulmonary bypass, while a control group of 29 patients were undergoing other major vascular, closed cardiac or thoracic surgery. Examinations were conducted pre-operatively, at 8 days and at 8 weeks post-surgery. A deterioration in post-operative neuropsychology score was defined as a fall in that patient's pre-operative level by a one standard deviation of the group distribution.

Eight CABS patients had pre-existing neurological conditions. At 8 days, 2 patients had visual field deficits, 1 of which persisted at 8 weeks (n = 67). At 8 days, 25% of the CABS group showed a drop in no more than 1 psychometric test, 50% showed a drop in 2-3 tests, and 25% showed a drop in 4 or more tests. Seventy-three subjects had a deficit in 2 or more tests at 8 days. At 8 weeks, 63% CABS patients showed no change, and 37% showed a drop in 2-3 tests. At 8 weeks, 50% of the comparison group had a deficit on two or more tests; however it is noted that the comparison group were older and generally sicker and more vulnerable.

Cerebral blood flow data are available for 59 of the CABS group. Mean blood flow is reported as being significantly reduced at 8 days post-surgery, but only in CABS patients. Blood flow had recovered by 8 weeks.

Muraoka (Ref. 41)
In other studies CT scans have been adopted to investigate sub-clinical changes in brain morphology. Muraoka reports the results of a study in which CT scans were conducted on cardiopulmonary bypass patients before and after surgery, with the objective of investigating differences between patients perfused with bubble oxygenators and those perfused with membrane oxygenators. Four of 27 patients operated on with bubble oxygenators showed changes in their post-operative CT scan (mean of 29 days after surgery), although there were no clinical neurological symptoms. By 6 to 8 months later no changes were apparent. There were no changes in the CT scans of the membrane oxygenator group (n=18). Muraoka concludes that the results suggest that microbubbles and microaggregates of more than 20 microns in size may be responsible for changes in CT scans.

Harrison (Ref. 27)
Harrison notes that it is significant that patients where the blood was passed through an additional filter, and whose incidence of emboli was 'less recordable' by Doppler, were less likely to show postoperative deterioration in performance on neuropsychological tests. This is taken as strong support for the view that consistently detectable neuropsychological deterioration in a proportion of patients after coronary bypass surgery is due at least in part to cerebral embolism.
4. ANALYSIS

4.1 INTRODUCTION

The objectives of this study have been to identify and assess any long-term health effects in the aviation, space medicine and cardiac surgery literature which may be relevant to concerns about long-term health deficits in divers. In order for the data presented in Section 3, on the outcomes of cardiac surgery, to be useful to this study’s objectives, it is necessary to consider:

• the validity of emboli in cardiac surgery patients as a model for emboli in divers.
• a method of quantifying and comparing the numbers of emboli observed to be present in divers and in cardiac surgery patients.
• a method of quantifying the observed CNS deficits in cardiac patients and cross-correlating this with the incidence of emboli in divers.

It is apparent that both the cardiac and the diving research communities have concerns about the presence of emboli in the blood and the consequent potential for damage to the central nervous system. In divers the initiating event is the separation from solution of an inert gas, normally nitrogen, which may then expand in volume within the venous system as further reductions in ambient pressure are experienced. It is also reported that in some divers who have a haemodynamically significant patent foramen ovale, emboli may cross over into the arterial circulation (Ref. 7). In cardiac surgery, gaseous emboli of both air and oxygen are present in the arterial system; those gaseous emboli which are formed of oxygen may be metabolised by the body. Both models experience the aggregation of platelets and other emboli of a biochemical nature. Cardiac emboli may also consist of foreign bodies, such as plastic debris, which have no apparent relevance to diving. The relevance of the cardiac model to diving is considered in section 4.2 below.

In order for the researchers to quantify the risk, Doppler ultrasound has been used by both research communities to monitor emboli; but there are differences in the physiological sites selected for monitoring and the grading systems adopted. Whereas the diving community has a preference to monitor the venous system at the pulmonary artery, cardiac researchers use transcranial Doppler, which monitors the cerebral arterial circulation. Diving researchers are accustomed to using either the Spencer (Ref. 42) or the similar Kisman-Masurel (Ref. 43) grading systems, whereas each cardiac surgical team has devised its own scoring system. Likewise both communities have used echocardiograms to monitor emboli in the heart, but grading systems are inconsistent. These inconsistencies of technique mean it is difficult at present to make an accurate quantitative comparison between the levels of emboli observed in divers compared to cardiac patients. However a tentative approach has been made in this paper with the objective of enhancing the value of the data available from the cardiac surgery literature (see section 4.2 below).

Likewise it is essential to be able to quantitatively assess the degree of impairment that may be associated with any given levels of emboli. This requires that common gradings of dysfunction are adopted. The various cardiac studies have some degree of commonality in their assessment of neurological and neuropsychological tests, but in order to explore this further, this study has attempted to ‘band’ test results by degree of impairment. This is described in section 4.3.
4.2 EMBOLI GENERATION AND CHARACTER

4.2.1 Embolic Mechanism In Diving

Emboli in divers are generated by the separation of an inert gas out of solution in the body, as ambient pressure decreases. Bubbles may form in the venous system, both intravascularly and in the tissues (extravascularly). These bubbles may expand in volume as ambient pressure decreases during decompression, and may be further increased in volume by the diffusion of inert gas into a pre-existing bubble. At the lower end of the scale, it is known that emboli 80μm in diameter are present in the venous system of divers. This is at the limit of detection of most ultrasound systems, and hence smaller emboli are likely to be present but undetectable.

Intravascular or extravascular bubbles may disrupt physiological function, either by mechanical compression of tissue, obstruction of blood vessels and subsequent ischaemic damage, or by compression of nerves. Furthermore, bubbles are known to activate leucocytes and platelets in the blood, which aggregate together and adhere to bubbles and the blood vessel lining. Complements i.e. proteins in blood serum, are also activated to destroy the foreign bodies i.e. the bubble. These complex biochemical reactions take place far removed from the original site of origin of the bubble, and are implicated in the appearance of symptoms of DCI, although the precise mechanisms are unclear (Ref. 44).

It is possible for bubbles in the venous system of the diver to enter the arterial circulation via a number of routes. The first of these is to cross the pulmonary circulation, which may occur when the normal filtration mechanism of the lung is overwhelmed by considerable volumes or rapid delivery of gas (see section 4.3.1 below). It may also be feasible for very small microbubbles to pass through the alveolar membrane of the lung. Secondly, gas may traverse across from the right to left side of the heart if the diver has a patent foramen ovale (PFO).

Emboli may then pass into the arterial circulation and reach the brain, which is the prime organ of concern for this study. Within the cerebral circulation emboli will be trapped if they form columns long enough to occupy several generations of branching arterioles such that the net surface tension pressure acting on the column exceeds cerebral perfusion pressure. This is stated as being most likely to occur in small arterioles (diameter 20-50 μm) between the white and grey matter of the brain (Ref. 44). This corresponds with what is known about the effectiveness of the lung as a filter (see section 4.3.1 below). Smaller bubbles are unlikely to become trapped because they split to form shorter gas columns. The trapping of bubbles in the brain is thought to be temporary; bubbles will eventually clear with successive cardiac systoles, and vasodilation will also occur as a response to bubble embolism (Ref. 44). However if bubbles do remain trapped, then ischaemia will result and cell death will occur. Despite the observation of bubble trapping as a temporary phenomenon, a progressive fall in brain blood flow has been seen after gas embolism. This may be due to the fact that bubbles may disrupt endothelial cells, resulting in increased permeability, loss of vascular regulation, and tissue oedema. An increase in blood viscosity due to the aggregation of blood constituents will also reduce tissue perfusion. Thus it is possible for decreased tissue blood flow, and hence ischaemic damage, to occur even in the absence of trapped bubbles.

In the diving situation gaseous emboli are known to persist for many hours after the end of the dive (Ref. 44). Being composed of an inert gas, they are not metabolised at cellular
level, but must be re-absorbed into the blood and tissue before being eliminated by the lungs. This process may take many hours, depending on the degree of supersaturation of inert gas present in the tissues. Likewise the formation of aggregates and coagulation will take several hours to resolve.

4.2.2 Embolic Mechanism In Cardiac Surgery

It has already been noted that emboli in the arterial circulation of a cardiac surgery patient are thought to be introduced by several mechanisms, including the formation of gas bubbles during extracorporeal circulation; air leaking around cannulae and inadequate de-airing of the heart prior to surgical closure; and the generation of arteriosclerotic debris and particulate debris from plastic tubing. In addition all of these mechanisms will provoke aggregates of fat, red cells, platelets or fibrin which may clump together in the blood stream, while similar aggregates will already be present in donated blood.

Data on emboli diameter are sparse, but the results of two studies where additional filtration in the arterial line was adopted during bypass offer some indication that emboli larger than 40μm diameter are implicated in CNS damage in cardiac patients. Aberg (Ref. 15) conducted trials which appeared to indicate that additional filtration with a 40μm pore size filter resulted in a reduced incidence of neuropsychological impairment. Pugsley (Ref. 21) conducted trials in which the use of a 40μm filter in the arterial line resulted in a marked reduction in high-intensity transcranial signals (HITS) during CPB, and in the subsequent incidence of neuropsychological deficit. It is probable that bubbles of less than 40μm diameter would still be present and would pass through the filter to enter the arterial circulation, but the incidence of observed CNS deficit from this insult appears to be lower than with larger bubble diameters. In a third study, Blauth (Ref. 24) identified the presence of retinal intravascular platelet-fibrin microaggregates in a dog model, of 20 to 70μm diameter.

It is therefore possible to speculate that emboli in cardiac surgery patients are in the range 20 to 70μm in diameter, but that those which appear to cause CNS deficits are likely to be greater than 40μm in diameter.

Duration of emboli during or following cardiac surgery is not reported. Gaseous emboli observed in cardiac surgery patients will be composed of a combination of 100% oxygen from the oxygenator, and of air from the surrounding atmosphere which will enter the open vasculature. Since oxygen has a higher solubility coefficient than nitrogen, and is metabolised quickly at cellular level, it is probable that those emboli formed of 100% oxygen will be relatively short-lived. It also seems reasonable to assume that all gaseous emboli will resolve rapidly, as soon as bypass is terminated and the chest has been closed, since the driving force for gas generation has been removed. Other particulate and aggregate material are likely to be more long-lived.

4.2.3 Comparison Of Diving And Cardiac Surgery Embolic Mechanisms

For the purposes of this study, it is possible to assert that the differences in the nature and character of emboli in divers and cardiac surgery patients are outweighed by the similarities, and that the cardiac surgery patient presents a viable model for the diver. This statement is based on the following considerations:
- Both populations are exposed to emboli in the arterial circulation. In divers these emboli are probably the result of indirect transfer from the venous system, whereas in cardiac surgery patients emboli are introduced directly into the arterial circulation. However the net effect is the potential to cause ischaemic damage to the CNS by the presence of emboli in the arterial system; this has been demonstrated in both populations.

- The assumed size of emboli which are present in both populations are broadly comparable (20 to 50μm diameter in the arterial circulation of a diver, 40 to 70μm in the cerebral circulation of a cardiac surgery patient).

- The introduction of gaseous emboli in the blood results in platelet and complement aggregation in both populations, thus aggravating the potential for ischaemic damage. The mechanism appears to be identical, regardless of the cause of the original insult.

- The fact that oxygen is a major constituent of gaseous emboli in cardiac surgery patients will tend to decrease the duration and size of these emboli, and thus the risk to cardiac patients of ischaemic damage. In contrast, inert gas in divers takes longer to resolve, thus placing the diver at a potentially greater risk.

- The introduction of particulate plastic debris in cardiac surgery patients has no comparison in diving. However this is only one of several sources of emboli in this population, and the cardiac surgery literature appears to place greater emphasis on the risk presented by gaseous emboli and subsequent biochemical effects.

- Cardiac surgery patients in general are exposed to only a single insult i.e. one surgical operation, whereas divers experience multiple exposures. Thus the diver may be at greater risk over the course of a career.

- It is not possible to factor out other sources of ischaemic damage in cardiac patients, e.g. low blood pressure during surgery. However the cardiac community have identified emboli as a key contributory risk factor, and data on CNS deficit in cardiac patients does correlate with the observed incidence of emboli. Therefore it appears valid to assume that the observed CNS deficits in cardiac patients are attributable in large measure to the presence of emboli.

4.3 GRADING OF EMBOLI

4.3.1 Ultrasound Data

Three studies have adopted transcranial Doppler techniques to monitor emboli during cardiac surgery involving cardiopulmonary bypass (CPB), and have presented data on numbers of emboli observed (Refs. 21, 26, 28). In order to be able to compare each study’s results and to relate this to diving research Doppler data, the scores from each study have been converted to a common ‘Emboli Grading’ as described below and shown in Table 9. This ‘Emboli Grading’ has been based upon the effectiveness of the lung in filtering out emboli in divers, and the number of embolic events observed over a defined number of heart cycles in cardiac surgery patients.

The Lung as a Filter

In deriving the table of comparative emboli gradings (Table 9), it has been assumed that in divers, the lungs act as an effective filter to screen out the vast majority of emboli in the venous circulation (Ref. 45). It is known that there are limits to this efficiency, in particular when pulmonary artery pressure is elevated and when large quantities of emboli are present (Ref. 46). But there is no agreed value for the efficiency of the lung as a filter in varying conditions (volumes of emboli present, differing pulmonary artery pressure etc.). Spencer (Ref. 47) demonstrated that it was possible for gas injected into the right ventricle of the
heart of a sheep to track across to the animal’s arterial system over a period of about 20 minutes (as monitored by Doppler). The effect on the animal varied from no observable symptoms to paralysis, unconsciousness and death, dependent on the volume and rate of gas injected. Spencer identified that gas emboli, at a dosage rate of 0.15 cc/kg/min, could traverse the pulmonary bed and was sufficient to produce Doppler signals in the arterial circulation in some animals. He did not quantify the volumes of gas observed in the arterial system.

Butler et al. (Ref. 46) indicates that venous air emboli are normally filtered in the lungs even when bubble diameters are as small as 21μm. This includes bubbles in the size range resulting from DCI (Ref. 48). However with an increase in pulmonary perfusion pressure caused by greater volumes of gas emboli, the driving pressure will force venous bubbles through the lungs, via large capillaries or small pulmonary shunts. This mechanism was apparent with injections of venous air infusions in dogs of 0.35ml.kg⁻¹.min⁻¹, at a pulmonary vascular pressure gradient of 34.7 ± 4.7mmHg. Again, the volumes of gas observed in the arterial system were not quantified.

What is clear from these studies and from the diving literature is that of any given quantity of emboli detected by Doppler in the venous circulation of a diver (at the pulmonary artery), only a small fraction of these emboli will enter the arterial circulation, with the potential to cause CNS damage.

However in cardiac surgery where CPB is adopted, the blood bypasses the lungs and heart, for oxygenation outside the body, before being returned to the arterial circulation. The only filtration undertaken is in the oxygenator and in any additional filters situated in the return line to the patient. Emboli detected in the cerebral circulation by transcranial Doppler during bypass are therefore a reasonably accurate representation of the total numbers of emboli present in the central nervous system, without the protection/reduction effect of filtration by the lung as seen during diver monitoring.

In order to be able to compare values for venous gas emboli (VGE) in divers monitored at the pulmonary artery before filtration by the lungs, and emboli in cardiac patients monitored directly in the arterial cerebral circulation, a correction factor has been assumed by the current study to account for the efficiency of the lungs in filtering out emboli in divers. This correction factor has been based upon the observations of Spencer and Butler (Refs. 47, 48). It is difficult to interpret their observations in a form which is relevant to the current study, bearing in mind that neither author quantifies the volume of gas observed in the arterial circulation following injection of known quantities of gas into the venous system. Hence it is not feasible to calculate an exact ratio for filtration efficiency. Moreover both diving and cardiac studies have quantified gas emboli in terms of number of observations of embolic events over a specific duration, rather than as volumes of gas. However for the purposes of this study an attempt has been made to quantify as a ratio the ability of the lung to filter out emboli.

Based on the implied statements that 99% of gas may be filtered out, but that “the lungs are a superb filter for bubbles under normal conditions” (Ref. 46) it has been arbitrarily assumed by this study that a factor of three orders of magnitude is the minimum ratio of effectiveness that might be expected. Hence it is assumed that the presence of any given number of emboli in the cerebral circulation of a cardiac patient represents 1000 more emboli in the lungs of a diver, e.g. one embolic event observed in the cerebral arterial circulation of a
cardiac patient would notionally equate to 1000 emboli in the venous circulation of a diver before filtration by the lungs.

If this assumed efficiency factor were to be greater e.g. by a further order of magnitude, 1:10⁴, it would imply that for each bubble in the arterial circulation of a diver, 10,000 are present in the lungs. This seems unreasonable in all except extreme cases of the chokes’ i.e. pulmonary DCI, and is not supported by diving experience which shows evidence of neurological impairment without the presence of clinical symptoms of DCI (Ref. 1). On the other hand, if the ratio of efficiency was significantly less, e.g. 1:10, one bubble in the arterial system would represent 10 bubbles in the lungs. This also seems unreasonable, given that the lungs ‘collect’ emboli from the whole body and it is well established that many bubbles are routinely observed by Doppler in the pulmonary artery of divers, without arterial gas being present. A factor of 10³ would therefore appear to be justifiable.

**Number of Cardiac Cycles in the Period of Observation**
When assessing emboli in divers, the grading systems used (Spencer or Kisman-Masurel) are based on the observation of VGE in each cardiac period. In order to be able to compare cardiac embolic events with VGE in divers, it has been necessary to estimate the number of cardiac cycles i.e. heart beats, in the cardiac surgery patient during the period of time during which Doppler monitoring was undertaken.

A notional value of 40 heart beats per minute has been adopted. This low value has been selected because in the majority of cardiac operations, hypothermic cooling has been used to reduce the metabolic rate and associated oxygen demand of the patient. Thus as an example, if the period of Doppler monitoring during surgery was 60 minutes, the assumed number of cardiac cycles over this period would be 60 x 40 = 2400.

**Emboli per Cardiac Cycle**
Combining these assumptions about the efficiency of the lung as a filter in divers, and the number of cardiac cycles in surgery patients during the period of Doppler monitoring, it is possible to derive a common ‘Emboli Grading’ based on the number of embolic events per cardiac cycle. This has been achieved by taking the mean figure of the range of number of embolic events quoted by each cardiac author, dividing this by the assumed total number of heart beats during the period of Doppler monitoring during surgery, and then applying the 1000:1 correction factor referred to above to account for the efficiency of lung filtration in divers.

For example, Pugsley (Ref. 28) adopted four ranges of numbers of microembolic events (MEE, see Glossary) over a 30 minute period. Taking the range 250-500 MEE per 30 minute period as an example calculation, a mean value of 375 MEE is assumed. At an assumed heart rate of 40 beats per minute for a duration of 30 minutes, the calculation is:

\[
\text{375 MEE} / (30\text{mins} \times 40 \text{ heart beats}) = 0.3125 \text{ emboli per cardiac cycle in the cardiac patient}
\]

Applying the lung efficiency correction factor enables us to equate this ‘score’ with the equivalent number of emboli present in the lungs of a notional diver:

\[
0.3125 \times 1000 = 312.5 \text{ emboli per cardiac cycle in the diver}
\]
Similar calculations have been made for each of the authors who present ultrasound data from cardiac surgery, on the basis of assumptions described in Table 9.

Two studies have used echocardiograms to monitor emboli within the heart (Refs. 16, 29). In Tingleff's study (Ref. 16), the echocardiogram observations were made during bypass, and hence the same correction factor has been applied as for transcranial Doppler to account for lung filtration in divers. In Oka's study (Ref. 29), the data refer to a period after bypass, when it is assumed that the patients' lungs are again acting as a filter; hence no correction factor has been applied (Table 9).

### Table 9
Basis of assumptions for converting cardiac Doppler data to 'emboli grading'

<table>
<thead>
<tr>
<th>Data from reference sources</th>
<th>Puglsey (Ref. 28)</th>
<th>Puglsey (Ref. 21)</th>
<th>Spencer (Ref. 26)</th>
<th>Oka (Ref. 29)</th>
<th>Tingleff (Ref. 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption 1</td>
<td>Heart rate of 40 beats/minute</td>
<td>Heart rate of 40 beats/minute</td>
<td>Heart rate of 40 beats/minute</td>
<td>Heart rate of 40 beats/minute</td>
<td>Heart rate of 40 beats/minute</td>
</tr>
<tr>
<td>Assumption 2</td>
<td>Mean for MEE count of &gt; 500 is taken as value of 1000, over 30 minutes</td>
<td>Mean for HITS rate of &gt; 1000 is taken as value of 2500, over 100 minutes</td>
<td>Duration of monitoring time is 2 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assumption 3</td>
<td>Correction factor applied for lung filtration effects</td>
<td>Correction factor applied for lung filtration effects</td>
<td>Correction factor applied for lung filtration effects</td>
<td>No correction factor applied</td>
<td>Correction factor applied for lung filtration effects</td>
</tr>
</tbody>
</table>

**Comparison with Doppler Scores**

By applying these various assumptions, a comparable grading structure has been devised (Table 10). This compares the classifications adopted by the various cardiac researchers with the Spencer and Kisman-Masurel grading systems used in diving research. Because of the inconsistency of the data, it has not been possible to undertake a direct conversion to diving Doppler scores. Instead the resulting value of emboli per cardiac cycle has been used to allocate a 'Low' or 'High' Emboli Grading. The cut-off for 'Low' or 'High' has been taken as 10 emboli per cardiac cycle. This has been derived from the Kisman-Masurel frequency parameter for grading of VGE in divers, where a rolling drumbeat of equal to or greater than 9 bubbles per cardiac period is graded KM Code 3. A KM or Spencer Grade of

---

3 MEE/HITS = high intensity transcranial signal count from Doppler monitoring of surgical patients. Signifies the presence of emboli in the arterial circulation.
III or IV in divers has already been demonstrated to be associated with a higher risk of DCI (Ref. 49).

At best, this interpretation gives an approximate indication of the quantities of emboli generated during cardiac surgery in a small population of subjects, and equates this to an equivalent number of emboli in divers. The results of this analysis are presented in Figure 1.

It can be seen that 226 of a total of 294 cardiac surgery patients undergoing either open heart procedures or coronary artery bypass grafting, normally with cardiopulmonary bypass, demonstrated emboli in the cerebral circulation (77%), as monitored by Doppler or echocardiograms. Of these, 189 patients (64%) had emboli which have been classed by this study as ‘High’ i.e. equivalent to a KM Doppler Grade III or IV.
Table 10  Corresponding Emboli Gradings and descriptions from diving and cardiac surgery studies

<table>
<thead>
<tr>
<th>EMBOLI GRADING</th>
<th>Spencer (Ref. 42)</th>
<th>Kisman (Ref. 43)</th>
<th>Spencer (Ref. 26)</th>
<th>Puglsey (Ref. 28)</th>
<th>Puglsey (Ref. 21)</th>
<th>Oka (Ref. 29)</th>
<th>Tingleff (Ref. 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 0 = no air emboli</td>
</tr>
<tr>
<td></td>
<td>Grade 0 = A complete lack of bubble signals</td>
<td>Frequency Parameters</td>
<td>No bubble emboli signals</td>
<td>No detectable microembolic events (MEE)</td>
<td>No detectable high intensity transcranial signals (HITS)</td>
<td>Grade 0 = no air emboli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade I = An occasional bubble signal discernible with the cardiac motion signal, with the great majority of cardiac periods free of bubbles</td>
<td>Code 0 = 0</td>
<td>Cumulative duration of signals of 0.1-0.5 seconds</td>
<td></td>
<td></td>
<td></td>
<td>Grade I = trace to moderate contrast air emboli lasting within 30 heart beats, seen less than 3 times during observation</td>
</tr>
<tr>
<td></td>
<td>Grade II = Many, but less than half, of the cardiac periods contain bubble signals, singly or in groups</td>
<td>Code 1 = 1 - 2</td>
<td>Cumulative duration of signals of 0.5-1 seconds</td>
<td></td>
<td></td>
<td></td>
<td>Grade II = Moderate contrast air emboli lasting more than 30 heart beats, seen 3 or more times during observation</td>
</tr>
<tr>
<td></td>
<td>Code 2 = several, 3 - 8</td>
<td>Code 3 = rolling drumbeat ≥ 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade II = Moderate contrast air emboli lasting more than 30 heart beats, seen 3 or more times during observation</td>
</tr>
<tr>
<td>HIGH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 0 = no air</td>
</tr>
<tr>
<td></td>
<td>Grade III = All of the cardiac periods contain showers of single-bubble signals, but not dominating or overriding the cardiac motion signals</td>
<td>Frequency Parameters</td>
<td>Cumulative duration of signals of 1-5 seconds</td>
<td>1-250 MEE per 30 minute period</td>
<td>HITS count ≤ 200</td>
<td>Grade III = Dense contrast air emboli lasts more than 30 heart beats, seen more than 3 times during observation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade IV = Maximum detectable bubble signal sounding continuously throughout systole and diastole of every cardiac period, and overriding the amplitude of the normal cardiac signals</td>
<td>Code 4 = continuous sound</td>
<td>Cumulative duration of signals of 5-25 seconds</td>
<td>250-500 MEE per 30 minute period</td>
<td>HITS count 201-500</td>
<td>Grade 2 = air that dominated the echocardiogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic duration of signals of 5-25 seconds</td>
<td>&gt; 500 MEE per 30 minute period</td>
<td>HITS count 501 - 1000</td>
<td>Grade 2 = air that dominated the echocardiogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HITS count &gt; 1000</td>
<td></td>
<td>Grade I = air that did not dominate the echocardiogram</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Type of Surgery</th>
<th>Total Number of Patients Monitored</th>
<th>Total Number of Emboli</th>
<th>Emboli Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Oka, Y. et al.</td>
<td>Coronary artery bypass grafting (CABG) with CPB</td>
<td>294</td>
<td>4</td>
<td>Total</td>
</tr>
<tr>
<td>1990</td>
<td>Pugliese, WB et al.</td>
<td>Coronary artery surgery with CPB - non</td>
<td>226</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>1991</td>
<td>Spencer, MP et al.</td>
<td>Coronary artery surgery (with CABG)</td>
<td>18</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>1990</td>
<td>Pugliese, WB et al.</td>
<td>Coronary artery surgery with CPB - non</td>
<td>15</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1990</td>
<td>Tingel, MD et al.</td>
<td>Cardiac valve operations with CPB</td>
<td>15</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1995</td>
<td>Tingel, MD et al.</td>
<td>Coronary artery bypass grafting (CABG)</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

NB: Patients' Emboli Grades are determined by MeSU (Masking) based on the number of patients monitored in the literature for frequency of bubble events.

Percentage of total number of patients (%):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>CABG</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>15</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>CABG</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>High</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
4.3.1 Retinal Angiography

A total of four studies have reported using retinal angiography during surgery to identify emboli in the CNS circulation (Ref. 19, 20, 23, 24). Due to lack of consistency in classifications and presentation of the data, it has not been possible to quantify or grade the numbers of emboli present. However, a total population of 135 patients monitored during surgery, 107 patients (80%) had emboli present in the retinal circulation (Table 11). This percentage is remarkably consistent with the reports from ultrasound techniques.

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>Author</th>
<th>Year</th>
<th>Total Number of Patients Monitored</th>
<th>Number of Patients with Emboli</th>
<th>% of Patients with Emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Blauth, C et al</td>
<td>1986</td>
<td>10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>23</td>
<td>Blauth, C et al</td>
<td>1988</td>
<td>21</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>19</td>
<td>Blauth, C et al</td>
<td>1989</td>
<td>40</td>
<td>31</td>
<td>78</td>
</tr>
<tr>
<td>20</td>
<td>Blauth, C et al</td>
<td>1990</td>
<td>64</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td>135</td>
<td>107</td>
<td>80%</td>
</tr>
</tbody>
</table>

4.4 NEUROLOGICAL/NEUROPSYCHOLOGICAL DEFICITS

4.4.1 CNS Deficits From All Cardiac Studies

A number of studies have examined cardiac patients before and after surgery by means of clinical neurological examination and batteries of psychometric tests. The period of re-test after surgery varies, with re-examination at one week and up to two months relatively common. Unfortunately for the purposes of this study, very few researchers have tracked patients over a period of years. Moreover, comparison of the results can be confused by the different definitions of severity of neurological insult which have been adopted. Three authors have adopted broadly comparable, but not identical, systems to classify deficits in performance at neuropsychometric test (Refs. 21, 32, 36, 37, 38). In addition, various authors have identified clinical neurological symptoms such as nystagmus and incoordination. In order to compare the various reported results, this study has adopted the following classification system, which has been adapted from the systems reported in the cardiac literature by combining clinical neurological signs and psychometric test results (Table 12). Where the neuropsychometric results reported in the literature do not permit classification according to this new scheme, the author's original classification, if one is given, has been retained. For example, Smith classes a degradation of one Standard Deviation in the individual's post-surgery score compared to his pre-surgery score in four or more tests out of a battery of ten as severe; Shaw defines severe as a deterioration of 1 SD in the individual's post-surgery score in five or more tests. In these circumstances Smith's own definition has been used to analyse his results.

Wherever possible, patients who are reported as suffering from stroke have been eliminated from the data, since it is considered that the cause of stroke in such patients may not be exclusively due to emboli and their inclusion might bias the results.
The analysis presented here has also excluded test results where the time lapse after cardiac surgery is less than one month. This is because it is recognised in the cardiac literature that some time is required for the patient to recover from the physical effects of anaesthetic agents and invasive surgery; neuropsychometric tests conducted before the patient has recovered from post-operative fatigue may be compromised. This recovery period is not defined in the literature, but since the purpose of this study is to examine long-term health effects after a cerebral embolic insult, a period of one month has been assumed to be the minimum appropriate recovery period.

Table 12
Classification of neurological/neuropsychological deficit

<table>
<thead>
<tr>
<th>Sign/Symptom/Test Performance Deficit</th>
<th>Grading of Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Score deterioration of 1 SD (calculated from pre-surgery group mean) in individual’s performance on 1-2 tests.</td>
<td>✓</td>
</tr>
<tr>
<td>Score deterioration of 1 SD (calculated from pre-surgery group mean) in individual’s performance on 3-4 tests.</td>
<td></td>
</tr>
<tr>
<td>Score deterioration of 1 SD (calculated from pre-surgery group mean) in individual’s performance on 5+ tests.</td>
<td></td>
</tr>
<tr>
<td>One or more of the following: ‘Soft’ neurological signs such as poor coordination, depressed reflexes, transient drowsiness, disorientation, persistent intellectual impairment. Focal nervous system lesions such as nystagmus, visual field deficits, double vision, extremity paresis, depression of consciousness.</td>
<td></td>
</tr>
</tbody>
</table>

It is apparent from Table 12 that within this classification system, the use of descriptions ‘Mild’ and ‘Moderate’ indicates an impairment in sub-clinical performance, as detected by neuropsychometric tests, with no clinical symptoms assumed. The descriptor ‘Severe’ indicates either a very marked reduction in psychometric test performance or the presence of clinical neurological symptoms. However it is important to note that this classification does not take account of subjective reports of forgetfulness, mental slowness or a reduced ability to concentrate. Shaw (Ref. 36) notes in passing that six months after surgery 40 patients (27%) complained of these symptoms, but despite this, only two patients are classified by her as having severe dysfunction. In the absence of confirmation that these symptoms were detectable at a formal clinical neurological examination, Shaw’s reported results have been adopted unchanged in this study.

It is also relevant to note that the number and choice of tests varied between the various studies. In general terms the neuropsychometric tests selected were sensitive to common aspects of cognitive function such as memory, attention, concentration, visuo-spatial ability and new learning ability. In those studies where only clinical neurological examinations were performed, any sub-clinical dysfunction will have passed unreported.
Analysis of the reports from the literature indicates that when the above classification is adopted, the percentage of cardiac patients with some degree of neurological or neuropsychological dysfunction varies between studies and between time frames. The mean percentage deficit at different sampling points varies from 4 to 58% (Figure 2). These deficits have been further analysed by degree, and the results are given in Figure 3. The overall incidence of dysfunction arising from all reported cardiac procedures is given in Table 13.

Table 13
Degree of neurological/neuropsychological dysfunction after cardiac procedures (all studies, from Figure 3)

<table>
<thead>
<tr>
<th>Follow-up Timing</th>
<th>Degree of Severity of Dysfunction - (%) of Patients Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>1 month</td>
<td>19</td>
</tr>
<tr>
<td>2 months</td>
<td>11</td>
</tr>
<tr>
<td>6 months</td>
<td>50</td>
</tr>
</tbody>
</table>

The apparent inconsistencies in these figures, for example an incidence of 1% severe dysfunction at 6 months, but not at two months, and an increase in moderate dysfunction between one and two months, is a reflection of the results from different studies, with patients being assessed by different methods, and at different time frames. The fact that some of the studies reported focused on the identification of clinical symptoms, and did not attempt to identify sub-clinical deficits may mask an even greater incidence of sub-clinical deficits. It is apparent from the analysis of results presented above and the reports in the literature that both clinical and test performance improves with time, but that in a percentage of patients some mild deficit is still apparent at up to two years.

4.4.2 CNS Deficits Associated With Emboli

Three research studies have combined the use of Doppler or echocardiogram monitoring with an assessment of the patients' neurological status. As reported above, where possible the original results of both the monitoring and the assessment of neurological status, have been graded by the current study to enable comparisons and correlations to be made. However only two of the three studies (Refs. 21, 28) have presented both ultrasound data and neuropsychological assessment data in a form which can usefully be interpreted for this study. The results are presented in Figure 4.

In both studies, the surgical team used bubble oxygenators, although in some patients additional filtration of the arterial line was used. All procedures were coronary artery surgery involving cardiopulmonary bypass. It can be seen that at two month follow-up, 28 out of a total of 134 patients exhibited continuing deficits in performance (21%), and that 12% of patients experienced 'moderate' dysfunction. The associated incidence of emboli graded 'High' can be seen from Figure 4 to be 100%. It is therefore possible to surmise that an overall incidence of Emboli Grade 'High' of 100% during surgery is associated with 21% of patients experiencing some dysfunction at up to two months post-surgery.
<table>
<thead>
<tr>
<th>Year</th>
<th>No. Authors</th>
<th>Author(s)</th>
<th>% Mild</th>
<th>% Mod</th>
<th>% Severe</th>
<th>% Mild</th>
<th>% Mod</th>
<th>% Severe</th>
<th>% Mild</th>
<th>% Mod</th>
<th>% Severe</th>
<th>% Mild</th>
<th>% Mod</th>
<th>% Severe</th>
<th>% Mild</th>
<th>% Mod</th>
<th>% Severe</th>
<th>% Mild</th>
<th>% Mod</th>
<th>% Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>61</td>
<td>President, J. V. et al.</td>
<td>1992</td>
<td>61</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1987</td>
<td>68</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1988</td>
<td>67</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1982</td>
<td>68</td>
<td>President, J. V. et al.</td>
<td>1993</td>
<td>61</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1987</td>
<td>63</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1988</td>
<td>64</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1983</td>
<td>69</td>
<td>President, J. V. et al.</td>
<td>1994</td>
<td>61</td>
<td>63</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1987</td>
<td>64</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1988</td>
<td>64</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1984</td>
<td>70</td>
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**Figure 3**: Incidence and Severity of Neuropsychological Deficit
Table I: The two tables for Figures 2A and 2B. Hodgson et al. 1999 are for two separate subgroups. However it was not possible to analyse the neurological assessment data for each.

<table>
<thead>
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<tr>
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<td>0</td>
<td>16</td>
<td>0</td>
<td>94</td>
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</tbody>
</table>

Figure 4: Patients Monitored with Doppler/echocardiogram, Combined with...
4.4.3 Comparison With Other Studies

The subjects in Pugsley's studies reported above were all undergoing coronary artery surgery with cardiopulmonary bypass, with or without filtration of the arterial line. It is possible to correlate his results with those of other surgical teams undertaking similar procedures i.e. coronary artery or coronary artery bypass grafting, and involving subsequent neurological or neuropsychological assessment, but who did not monitor their patients for emboli. The results of this analysis are shown in Figure 5. It should be noted that all studies apart from those of Shaw used bubble oxygenators. Shaw used bubble oxygenators for 106 operations, and membrane oxygenators for the remaining 206 procedures; it has not been possible to group the neurological results reported by Shaw to 'bubble' and 'membrane' sub-groups. Given that membrane oxygenators are believed to reduce numbers of emboli, inclusion of these data will tend to reduce the incidence of associated neurological deficit.

Analysis of the data indicates that at one month after surgery patients experience a 73\% incidence of neuropsychological deficit, surgery, reducing to 31\% at two months. At six months after surgery, there is an apparent increase to 57\% incidence of deficit. However as already noted above, the variation in the percentage of patients who demonstrate dysfunction varies with timescale, depending on which studies are included at each sampling point. This accounts for the apparent increase in incidence of deficit at six months, which is based on the results of a single study. It is also possible that some dysfunction may only manifest itself some time after the insult. Factors such as whether additional filtration of the arterial blood is adopted can influence the neurological outcome (Ref. 28). In the majority of cases these deficits are mild or moderate in severity, but two patients have been graded as having a severe deficit.

On this premise, it is possible to surmise that a 31\% incidence of deficit at 2 months after surgery (from coronary artery procedures, Figure 5) is linked to an incidence of 100\% of 'High' Emboli Grades during this same type of surgical procedure (from Figure 4). Given the results reported by Shaw (Ref. 36) the actual incidence of deficit may be even higher, in the region of 50\%-60\%.

If this comparison is extended to diving, it is possible to suggest that over 30\% of those divers who experience VGE graded III or IV, that is the equivalent of a 'High' Emboli Grade during surgery, may be at risk of some degree of CNS dysfunction. The degree of dysfunction will vary from clinical neurological symptoms to sub-clinical deficit, depending on the degree of insult and time lapse and recovery since time of insult.

Data on patterns of recovery amongst cardiac patients are few after about six months post-surgery. However there is limited evidence to suggest that CNS dysfunction remains for up to five years after surgery (Refs. 17, 31). Sotaniemi (Ref. 31) reports that 21 out of 44 patients (47\%) who were re-assessed five years after surgery displayed a statistically significant decline in performance on aspects of the neuropsychological test battery which examined frontal lobe ability, learning and recognition.
Assessment of Neuropsychological Functioning of Coronary Artery Surgery Patients, combined with Neuropsychological Testing.

Figure 5. Coronary Artery Surgery Patients, combined with Neuropsychological Testing.
5. DISCUSSION

5.1 AVIATION AND SPACE MEDICINE

The apparent lack of any references within the aviation and space medicine literature to research on the potential of ‘silent’ bubbles to cause long-term health effects is surprising. It is, however, confirmed by personal communication with experts in the field. Current space and military research is directed towards the short-term success of the mission, consistent with the immediate welfare of personnel. The objective of much current work is to explore the limits at which high altitude flights or extravehicular activities can be conducted before operational problems (i.e. DCI) are encountered. Where health concerns arise, they are focused on the prevention of clinical symptoms of DCI.

HSE’s objective for diving safety is to prevent acute and chronic health deficits caused by the working environment. While the aerospace community offers valuable insight into the prevention and treatment of acute health deficits, it presents little new information on chronic, long-term effects. There are, however, opportunities for the two research populations to collaborate in order to enhance their mutual understanding of the long-term health implications of exposure to emboli.

5.2 CARDIAC SURGERY

Review of the cardiac surgery literature reveals several similarities to the diving experience. There is common concern that emboli, either gaseous, or particulate, may cause ischaemic damage to the brain. Retinal angiography, transcranial Doppler and echocardiograms have confirmed the presence of emboli in the arterial circulation of cardiac patients. While it is not possible to differentiate between gaseous and other emboli in cardiac patients, it is known that divers also experience fat emboli and other aggregates in the blood stream, generated by the biochemical reaction to foreign bodies i.e. bubbles. Thus there is a similarity in the character of emboli observed in both populations, and the overriding common factor is ischaemia due to the presence of emboli in the arterial blood supply. Thus while the initiating event may be different, the consequences appear to be very similar in both divers and cardiac surgery patients.

Other risk factors in cardiac surgery are proposed to be low arterial blood pressure, failure of oxygenator equipment, use of bubble rather than membrane oxygenators, inadequate filtration of the blood during bypass, and long-duration bypass procedures. It is difficult to identify any commonality with diving, apart from supposing that such risk factors may result in hypoxia, and hence ischaemic brain damage.

The most comprehensive studies of intellectual impairment following cardiac surgery are those of Shaw and the various studies by the combined groups at the Middlesex and Hammersmith Hospitals, London (Arnold, Blauth, Harrison, Pugsley, Newman, Smith, Treasure). Shaw identifies that other factors such as pre-existing disease are correlated with impairment, but provides no evidence that emboli during surgery may be a factor. This may in part be due to the fact that her study did not directly monitor emboli during the operation. The identified correlation with vascular disease may be an indication that certain patients are at increased risk of emboli, and consequent cognitive deficit. On the other hand the Middlesex and Hammersmith groups provide clear indications from transcranial Doppler and retinal angiography that emboli are present during the great majority of cardiac
procedures. While there is no proven link that cognitive dysfunction is solely attributable to the presence of emboli during surgery, there is substantial evidence to link retinal infarcts and high Doppler scores with post-operative intellectual impairment.

It is apparent that differences in surgical technique and in post-operative assessment will influence the apparent incidence of CNS dysfunction. Shaw, for example, identifies a significantly greater level of deficit at one month post-surgery (79%) than Pugsley (52%), despite the fact that two-thirds of the patients in Shaw’s study had a membrane oxygenator, which is assumed to reduce the levels of emboli. On the other hand, half of Pugsley’s subjects were operated on with the benefit of additional filtration, which he identifies as contributing to a reduction in the numbers of emboli (this sub-group of patients had an incidence of deficit of 15%). Shaw is the only investigator to have reported in full on the results of neuropsychometric tests at six months after surgery, when he identified deficits in 57% of patients. It is possible that in the light of Shaw’s findings, the incidence of deficit quoted by Pugsley may be underestimated. In the medium to longer term, an incidence of deficit of over 45% has been reported by a single study (Ref. 31).

While the evidence suggests that diffuse microemboli may impair neurologic function without producing visible cerebral infarctions, it is a weakness of the cardiac surgery studies that the attempts to quantify levels of emboli during surgery do not adopt a common grading system. It has been noted that the cardiac studies have adopted transcranial Doppler to monitor emboli in the cerebral circulation, whereas diving studies have used precordial Doppler. It is recognised that the two sites are not directly comparable. These factors make it difficult to directly compare diving and cardiac studies, or to correlate ultrasound results with other studies’ tests of cognitive function. The preliminary analysis undertaken in this study, with some way to overcoming these difficulties, by factoring the cardiac Doppler and echocardiogram results where appropriate to do so, and adopting a common grading system for emboli from cardiac and diving studies. This way it has been possible to correlate the results from surgical procedures where ultrasound was used to quantify emboli, with diving studies.

At the same time it has been possible to adopt a common grading system for neurological/neuropsychological insult for cardiac studies. When the results of these studies are cross-correlated with the analysis of emboli grades from cardiac surgery, it is possible to link an 100% occurrence of ‘High’ emboli scores with at least a 30% incidence of neurological insult at two months after surgery. This may be an underestimate if Shaw’s findings are considered, and the actual incidence may be as high as 50-60%. The degree of deficit is in the majority of cases classed as ‘mild’ cognitive impairment, at up to 6 months beyond the operation. In a limited number of cases the dysfunction is more severe, with clinical neurological symptoms which may be disabling. It is important to recognise that ‘mild’ dysfunction, indicating a sub-clinical deficit in performance on neuropsychometric tests, may be an acceptable outcome from life-threatening disease and related heart surgery. It is not an acceptable outcome from occupational exposure i.e. diving decompression. Therefore the suggestion from this study, that over 30% of divers who experience VGE graded III or IV may be at risk of this level of neurological impairment, is of concern.

It has not been possible to factor out other possible causes of neuropsychological deficit such as low perfusion pressure during surgery, nor to identify with any precision the levels of deficit which occur on a longer timescale. However it is clear that the cardiac community considers that a major contributing factor is the presence of emboli during bypass, and that there is some continuing deficit in a substantial proportion of cardiac patients. Moreover it is
pertinent to note that the nature of symptoms or neuropsychological results are very similar in both populations, with reports of cognitive failures, lapses of concentration, and poor memory being common to both.

When these tentative conclusions are compared with diving research studies, it is apparent that there are similar trends. It has already been proposed in the diving literature that sub-clinical neurological deficits are associated with a history of DCI (Refs. 1, 2, 3, 4, 5, 6). The incidence of deficits identified in divers by these studies are in the region of 20% to 30% (for tests of neurological function, integrity of sensory nerve pathways and cerebral blood flow). Other work indicates that Doppler Grades III and IV correlate with an increased risk (10 to 21%) of DCI (Ref. 49). In an analysis of diving trials and data from offshore, Robertson (Ref. 50) proposed that a bubble cm$^{-1}$ sec$^{-1}$ (BCS) score over a period of two hours which was greater than 2.5 (BCS{2 hours} > 2.5) carried a 4% risk of symptoms of DCI. He went on to suggest that approximately 6% of air dives offshore in the UK sector of the North Sea may be generating levels of VGE associated with this level of DCI risk. Cardiac surgery studies have confirmed that the equivalent Emboli Grading to Doppler Grade III/IV correlates with a high risk of CNS insult. It would therefore appear that these indicators of DCI risk from diving (Doppler grade III/IV; BCS{2 hours} > 2.5) are associated with at least a 30% incidence of CNS damage.

These predictions are based on certain key presumptions. One of these is that the nature of the emboli in cardiac patients is similar to those in divers, or at least that the nature of ischaemic damage caused by emboli is the same. This would appear to be valid, based on the fact that many of the cardiac reports confirm the presence of air bubbles, and comment that the nature of the emboli is immaterial to the CNS outcome. It is also known that the presence of gaseous emboli in the venous circulation of divers gives rise to the accumulation of other debris such as fatty emboli, platelets etc. These are similar in nature to non-gaseous emboli in cardiac patients (with the exception of 'foreign' debris such as plastic introduced by the surgical equipment). It is also relevant that Spencer, who is the sole researcher to report in both areas of interest, confirms that the quality of the bubble detected by Doppler during cardiac surgery is similar to those in diving subjects.

A second key assumption is the accuracy of the factor adopted in this study for the efficiency of the lung as a filter. If the factor of 1000 assumed here is an underestimate by an order of magnitude, this would imply that very large numbers of emboli would need to be present in the lungs of divers for CNS deficits to be incurred. This would affect the analysis undertaken by this paper because such a level of 'bubbling' is likely to occur in only 'worst case' decompression incidents, and hence the predicted risk of CNS deficit would be very low. However despite the fact that such incidents are rare, neurological deficits have been identified in divers, even those who have not experienced DCI in any form. This scenario therefore appears to be unlikely.

On the other hand, a ratio of 1:10 for lung filtration efficiency would reinforce the findings of this paper because it would imply that a very small number of bubbles in the lungs of a diver would result in the presence of arterial emboli, with an associated risk of CNS deficit. Thus even a Doppler score of I or II would present a definable risk to the CNS. Alternatively, since it is known that significant microemboli can be present in the lungs of a diver following a non-provocative decompression, a low ratio might imply that substantial numbers of bubbles will then traverse across the pulmonary bed. This would again present a risk of CNS damage, associated with Doppler Grade I or II. Either hypothesis appears
unrealistic in view of the literature reports of pulmonary efficiency, and the fact that if they were to be true, many more divers would present with sub-clinical symptoms.

It is also relevant to consider the implications of a patent foramen ovale (PFO) in divers, and the associated potential risk of subsequent brain lesions. There is evidence to suggest a possible link between the presence of a PFO and subsequent decompression illness (Refs. 50, 51, 52). However the role of a PFO in decompression illness is unclear (Refs. 1, 53). In theory the presence of a PFO will increase the likelihood of producing arterial emboli. Field trials have apparently failed to confirm this (Ref. 53); in this study transcranial Doppler monitoring was undertaken on a number of divers after dives involving in-water stops and surface decompression. Monitoring was continued for intervals of between 1.5 and 23 minutes after surfacing. However the apparent absence of arterial gas emboli in this study may be attributable to the fact that monitoring ceased shortly after surfacing. Other trials have demonstrated that there is a latency period before emboli are formed in the circulation (Refs. 54, 55, 56).

A recent study (Ref. 7) has reported an increased prevalence of multiple brain lesions in divers with a PFO compared to divers without a PFO. These multiple lesions occurred exclusively in divers whose PFO was 'of high haemodynamic relevance' and were present without any episodes of Type 2 DCI being reported by the subjects. It is therefore possible to speculate that the presence of a haemodynamically significant PFO may contribute to the presence of 'silent bubbles' and subsequent sub-clinical lesions. If this is a valid assumption, the cardiac model may assume greater relevance to diving because it reinforces the view that microemboli present in the cerebral circulation will cause sub-clinical neurological deficit in a proportion of those persons at risk.

It is noteworthy that whereas the cardiac patient is normally only exposed to a single event i.e. one operation, the diver experiences multiple exposures during the course of a career. This may place him at greater long-term risk, on the assumption that frequency of exposure may result in cumulative damage.

The cardiac literature confirms that retinal angiography may be used as a technique to identify deficits in arterial blood flow, and that there is a tentative link between retinal lesions and cognitive impairment in coronary bypass patients. This is of value in supporting HSE's proposed strategy of validating the use of retinal angiography to identify lesions caused by a non-convulsive decompression, and to use retinal angiography as a technique to identify the presence of lesions and to correlate this with diving exposure and neurophysiological test results.

5.3 FURTHER WORK

The current study has not identified any cardiac studies in which patients are monitored for neurological and neuropsychometric deficits beyond five years after surgery. In the early study of Javid (Ref. 17), 4% of patients are reported as having continuing mild dysfunction at two years after their operation. However the sample size was small and sub-clinical deficits were not investigated. In a later study by Sotaniemi (Ref. 31) it is reported that some patients continued to display clinical and sub-clinical CNS dysfunction at five years after surgery, but it is not possible to correlate this observation with the nature of CNS insult experienced by these patients. The need therefore remains to improve understanding of the repair mechanisms which may contribute to recovery, the time course of recovery following differing degrees of insult, and the implications for future quality of life. This will
be of assistance in assessing the potential risk to divers' long-term health following a similar neurological insult.
6. CONCLUSIONS

1. Review of the cardiac surgery literature indicates that where Doppler or echocardiogram techniques have been used to monitor emboli in cardiac patients undergoing coronary artery surgery, the presence of emboli is confirmed in all patients. The emboli observed during a decompression in divers and during surgery in cardiac patients are both implicated in ischaemic damage within the central nervous system, in particular in the brain. Thus the cardiac surgery patient appears to be a valid model for assessing the potential of emboli to cause cerebral deficits in divers.

2. The levels of emboli generated by surgery have been graded as 'High' by this study. Analysis of Doppler and echocardiogram data from cardiac studies suggests that 'High' levels of emboli during surgery are equivalent to a Doppler score of KM Grade III/IV in diving subjects. These levels of emboli during surgery appear to be associated with at least a 30% incidence of neurological/neuropsychological deficit, and the actual incidence may be as high as 50-60% at two months after surgery.

3. Previous studies indicate that this level of 'bubbling' i.e. Doppler grades III and IV, may be present after some 6% of operational offshore air dives. Hence it is probable that the same degree of cerebral deficit as observed in cardiac patients will exist in over 30% of those divers who undertake these more stressful dives. This is indeed confirmed by research investigating CNS damage in divers.

4. The neurological symptoms reported or observed in cardiac patients following surgery appear to be comparable with those reported in divers. These deficits are both clinical and sub-clinical in nature, consisting of: focal neurological lesions such as visual field defects and paresis; 'soft' neurological signs such as poor co-ordination, depressed reflexes and disorientation; and cognitive impairment such as reduced memory function, loss of new learning ability and lapses of concentration.

5. The long-term duration of the deficit is not known, but there are reports of over 50% of patients continuing to demonstrate sub-clinical cognitive deficits at 6 months after surgery. The results of a single study indicate that this level of deficit may persist up to five years after the original insult. If this pattern is also present in divers, as predicted by this study, it is of concern that such damage is the result of occupational exposures; that divers may experience multiple exposures; and that the damage may persist long after the original insults.

6. These findings support OSD's concern about the potential of asymptomatic 'silent bubbles' to cause subsequent CNS damage. They confirm the current direction of OSD diving research strategy, namely to endeavour to reduce levels of gas during a decompression and to investigate the prevalence of CNS deficits in divers.

7. These findings are based on the assumptions, believed to be justified, that:
   • despite some differences in the character of the emboli generated during cardiac surgery compared to those evident in divers during a decompression, the effects of these emboli and the mechanism of ischaemic damage remains the same;
   • the evidence of CNS deficits in cardiac surgery patients is attributable largely to the presence of emboli in the arterial system, although it is recognised that there are other mechanisms which may contribute to ischaemic damage;
8. Further work is required to improve understanding of any repair mechanisms and the
time course of possible recovery following the type of neurological insult experienced
by divers. A key requirement is to determine the percentage of subjects who
experience permanent dysfunction and to assess the implications for their future quality
of life.

9. Cardiac teams have demonstrated the use of psychometric tests to assess the
neuropsychological status of patients after surgery. This would appear to confirm the
suitability of such techniques for assessing possible cognitive impairment in divers.

10. An intensive search of the aviation and space medicine literature, and communication
with experts in these fields, indicates that the aerospace community have not
investigated the potential of emboli during decompression to cause long-term health
effects.
REFERENCES


8. Dixon GA, Adams JD and Harvey, WT. (Undated) *Decompression sickness and intravenous bubble formation using a 7.8 psi simulated pressure-suit environment.* School of Aerospace Medicine, Brooks Air Force Base, Texas.


13. Webb JT and Pilmanis AA. 1993. *Breathing 100% oxygen compared to 50% oxygen: 50% nitrogen reduces altitude-induced venous gas emboli.* Aviation, Space and Environmental Medicine, Sept. 1993, 64 (9 Pt 1) pp 808-12.


## GLOSSARY

<table>
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<tr>
<th>Term</th>
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<td>Anoxia</td>
<td>No oxygen in the tissues.</td>
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<td>Arteriosclerosis</td>
<td>Degenerative arterial change, primarily a thickening of the middle coat of the vessel.</td>
</tr>
<tr>
<td>Atheroma</td>
<td>The deposition of hard plaques of lipoid material in the intimal layer of the arteries.</td>
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<tr>
<td>Atherosclerotic vascular disease</td>
<td>Co-existing atheroma and arteriosclerosis.</td>
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<tr>
<td>BCS</td>
<td>The concentration of inert gas bubbles observed in the pulmonary artery, expressed as bubbles per square centimetre per second (bubbles cm$^{-2}$ sec$^{-1}$).</td>
</tr>
<tr>
<td>BCS {2 hours}</td>
<td>Bubbles cm$^{-2}$ sec$^{-1}$, totalled over two hours. Four Doppler scores, recorded once in each of four half hour time ranges, summed to give a total figure over a two hour period.</td>
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<td>Cardiac bypass</td>
<td>Use of a temporary mechanical pump to maintain the blood circulation during a heart operation.</td>
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<tr>
<td>Cardiopulmonary bypass</td>
<td>The avoidance of circulation of blood through the heart and lungs by the use of an artificial pumping device, so as to allow unimpeded heart surgery or heart transplantation. The pumping device includes rotary pumps to maintain the circulation through the body, blood filters for particles, bubbles and foam, a blood oxygenator and carbon dioxide extractor, a cooler and re-heater. Blood from the patient's main veins is carried in tubes to the machine and the machine output is connected to the main artery (the aorta).</td>
</tr>
<tr>
<td>Cardiotomy</td>
<td>Cutting into the heart.</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>Pertaining to the blood vessels of the brain.</td>
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<tr>
<td>Cerebrovascular accident</td>
<td>Interference with the cerebral blood flow due to embolism, haemorrhage or thrombosis.</td>
</tr>
<tr>
<td>Complement</td>
<td>A normal constituent of plasma, of importance in immunity mechanisms, as it combines with antigen-antibody complex to complete the body's reaction against bacteria.</td>
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<tr>
<td>Coronary artery bypass (CAB) or coronary artery bypass grafting (CABG)</td>
<td>The use of a short length of vein to connect the aorta to a point on a coronary artery beyond a narrowing or obstruction.</td>
</tr>
<tr>
<td>CT scanning</td>
<td>Computer assisted tomography. Internal X-ray scanning in which an image is built up by a computer from data derived by analysing and correlating the output from thousands of separate serial, low intensity readings, taken in successive thin planes.</td>
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<tr>
<td>Doppler</td>
<td>The use of ultrasonic waves to detect bubbles in the bloodstream. Ultrasonic waves are scattered and shifted in frequency by bubbles moving in the blood. The output is in the audio frequency range and is detected by human observers.</td>
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<tr>
<td>Echocardiogram (echocardiography)</td>
<td>A form of ultrasound imaging used to investigate the movement and action of the heart.</td>
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<tr>
<td>Emboli</td>
<td>Material carried in the bloodstream to a point where it causes obstruction to the blood flow. In divers these commonly consist of bubbles of inert gas during a decompression; in both divers and non-divers the emboli may consist of cholesterol, bone marrow, fat.</td>
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<tr>
<td>Endarterectomy</td>
<td>An operation to restore full blood flow in an artery narrowed or blocked by atherosclerosis, by removing the diseased inner lining and any associated blood clot.</td>
</tr>
<tr>
<td>Endothelial</td>
<td>Lining membrane of the heart, blood and lymph vessels.</td>
</tr>
<tr>
<td>Fibrin</td>
<td>Matrix on which a blood clot is formed.</td>
</tr>
<tr>
<td>HITS</td>
<td>High intensity transcranial signal count from Doppler monitoring of surgical patients. Signifies the presence of emboli in the arterial circulation.</td>
</tr>
<tr>
<td>Hypofusion</td>
<td>Diminished blood supply.</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>Inadequate blood flow to any part of the body, which may result in local tissue death (infarction).</td>
</tr>
<tr>
<td>Leukocyte</td>
<td>White corpuscles of the blood.</td>
</tr>
<tr>
<td>Macula</td>
<td>Spot on the retina which is the area of clearest central vision.</td>
</tr>
<tr>
<td>MEE</td>
<td>Microembolic event, observed by transcranial Doppler monitoring of surgical patients. As for HITS.</td>
</tr>
<tr>
<td>Microvascular occlusions</td>
<td>Closure or blockage of the small blood vessels.</td>
</tr>
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<td>Term</td>
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</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Motor hemisindrome</td>
<td>Symptoms pertaining to movement or action of one side of the body.</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Involuntary and jerky repetitive movement of the eyeballs.</td>
</tr>
<tr>
<td>Ocular fundi</td>
<td>The portion of the eye furthest from the cornea, consisting of the retina and choroid coat.</td>
</tr>
<tr>
<td>Oedema</td>
<td>Abnormal infiltration of the tissues with fluid.</td>
</tr>
<tr>
<td>Paresis</td>
<td>Partial or slight paralysis; weakness of a limb.</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>An opening in the partition between the right and left upper chambers of the heart.</td>
</tr>
<tr>
<td>(PFO)</td>
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<tr>
<td>Precordial</td>
<td>Pertaining to the area of the chest immediately over the heart.</td>
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<tr>
<td>Retina</td>
<td>Light-sensitive internal coat of the eyeball.</td>
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<tr>
<td>Retinal angiography</td>
<td>Demonstration of the arterial system within the retina of the eye after injection of an opaque medium</td>
</tr>
<tr>
<td>Silent bubbles</td>
<td>Gas bubbles in the bloodstream which produce no detectable symptoms of decompression illness.</td>
</tr>
<tr>
<td>Spencer Grade</td>
<td>A classification scheme for monitoring gas bubbles in the blood using Doppler techniques, developed by MP Spencer. The Spencer code grades bubbles on a scale 0 to IV, based on the number of cycles containing bubbles.</td>
</tr>
<tr>
<td>Systole</td>
<td>The contraction phase of the cardiac cycle (as opposed to diastole).</td>
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<tr>
<td>Transcranial</td>
<td>Through that part of the skull enclosing the brain.</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>A method of body imaging using high frequency sound, which is based on the reflectivity of sound.</td>
</tr>
<tr>
<td>Vascular</td>
<td>Supplied with vessels, especially referring to blood vessels.</td>
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<tr>
<td>Venous gas emboli</td>
<td>Inert gas bubble formed in the venous circulatory system.</td>
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<td>(VGE)</td>
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<tr>
<td>Unilateral hyperreflexia</td>
<td>Excessive reflexes, relating to or on one side only.</td>
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APPENDIX 1

SUMMARY OF AVIATION AND SPACE MEDICINE ARTICLES
RELEVANT TO LONG-TERM HEALTH

PREVALENCE OF DECOMPRESSION SICKNESS AMONG U-2 PILOTS

Authors: Bendrick, GA; Ainscough, MJ; Pilmanis, AA; Bisson, RU.
Aviation, Space and Environmental Medicine, Mar 1996, Vol. 67 No 3, p199-206.

Though it is rarely reported, decompression illness is an expected risk for U-2 aviators. The potential for chronic sequelae of untreated DCI in this population has never been addressed. A cohort of 416 U-2 pilots (active-duty and retired) were mailed two sequential anonymous surveys to assess demographic data, career prevalence of DCI symptoms, and overall health status with an emphasis on chronic musculoskeletal problems. During their career 75.5% of those pilots who responded (over 60%) experienced DCI symptoms such as joint pain, skin manifestations, and/or neurological problems. The association of past DCI with current arthritic problems was not statistically significant. 11% of respondents reported affirmative responses to past or recurring neuropsychological problems, but there was no statistical link to prior DCI symptoms, and the paper does not discuss any aspect of neurological or neuropsychological health.

CHANGES IN THE CENTRAL NERVOUS SYSTEM AND THEIR CLINICAL CORRELATES DURING LONG TERM SPACEFLIGHT

Author: Newberg, AB.

This paper reviews current literature on the metabolic, neurotransmitter and morphological changes that occur in the CNS during long duration space-flight. The concept of detrimental reversible or irreversible effects on the brain, and psychological and cognitive dysfunction is identified. However no evidence of long-term, post-flight deficits is presented.

LONGITUDINAL STUDY OF ASTRONAUT HEALTH: MORTALITY IN THE YEARS 1959-1991

Authors: Peterson, LE; Pepper, LJ; Hamm, PB; Gilbert, SL.

This study undertook a historical cohort study of mortality among 195 astronauts who were exposed to space and medical sources of radiation between 1959 and 1991. Overall it was found that astronauts are at a health disadvantage from catastrophic accidents (standardised mortality ratio (SMR) of 1346 for fatal accidents). The study does not address the health consequences of decompression.
CONCEPTS FOR NASA LONGITUDINAL HEALTH STUDIES

Authors: Nicogossian, AE; Pool, SL; Leach, CS; Moseley, E; Rambaut, PC.
Aviation, space and Environmental Medicine, Dec. 1983, pS68-S72.

This paper presents concepts for cross-sectional and longitudinal studies of future astronauts. The cumulative effects of radiation, bone demineralisation and identification of environmental/human factors characteristics as they might affect physiological responses to living and working in space, are identified as worthy of study. There is no indication in the paper that neurological dysfunction or the generation of gas emboli during training or actual space flight is considered a problem.

Clinical data collected from a 15-year study of pre-Shuttle astronauts have revealed no significant long-term effects from space flight. However it is stated that very little information is available concerning the short and long-term medical consequences of long duration exposure to space and subsequent readaptation to the Earth environment.

LONG-TERM FOLLOW UP OF ASTRONAUT HEALTH INDICES

Authors: Nicogossian, AE & Moseley, E.

This paper describes preliminary 10-year findings of prospective studies of astronaut medical evaluations, established in 1977, and results obtained on data accumulated prior to 1977. The objective was to develop medical selection and retention standards and to establish long-term astronaut follow-up studies in order to assess long-term career implications on the health of individuals who work and live in space. Variables assessed included hearing, biochemistry, blood pressure, heart rate, respiration, vision, intraocular pressure, and body size. Variables for future assessment include effects of lifestyle, level of exercise, pulmonary function, radiation exposure and time spent in space. Gas emboli or decompression is not identified as a risk factor.

MEDICAL MANAGEMENT OF US ASTRONAUTS

Author: Billica, R.
Journal of Clinical Pharmacology 1994; 34: 510-512

This article describes the medical management of US astronauts, including medical monitoring, intervention, psychosocial support and environmental health monitoring.
Medical hazards of space flight are identified as:

<table>
<thead>
<tr>
<th>Zero-gravity</th>
<th>Psychological stress</th>
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<tr>
<td>Fluid loss</td>
<td>Nutritional deficiency</td>
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<tr>
<td>Haematological and immune system changes</td>
<td>Infectious disease</td>
</tr>
<tr>
<td>Neurovestibular degradation</td>
<td>Radiation</td>
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<tr>
<td>Musculoskeletal degradation</td>
<td>Vacuum (decompression illness)</td>
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<tr>
<td>Cardiovascular changes</td>
<td>Noise/vibration</td>
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<tr>
<td>Electrolyte changes</td>
<td>Toxic exposure</td>
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<tr>
<td>Illness</td>
<td>Trauma</td>
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<td>Space motion sickness</td>
<td>Endogenous illness</td>
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<td>Isolation/confineimet</td>
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