The Potential Role of Oxygen in the Prevention of Neurologic Deficits After Cardiac Surgery

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Abstract

Cardiac surgery using cardiopulmonary bypass (CPB) has become an everyday procedure. While massive air embolism during open heart surgery is a rare accident, there is a growing body of clinical and experimental evidence pointing to the fact that cerebral microbubble embolism is common. These microbubbles are not harmless and may be responsible for the neurologic and neuropsychological deficits which affect the quality of life and productivity of a considerable number of patients after the operation, a phenomenon popularly called a "pump head". Decompression sickness (DCS) affecting divers is another clinical situation in which arterialized microbubbles may cause cerebral deficits. Since hyperbaric oxygen (HBO) is considered a specific therapy for overt air embolism, as well as for DCS, we suggest that this mode of therapy may also be applicable to subtle microbubble embolism resulting from CPB. HBO therapy is simple, safe, and inexpensive. It can be delivered in a monoplace hyperbaric chamber in the recovery room immediately after the operation. If an HBO facility is not immediately available, or if the operating team is reluctant to use HB in hemodynamically unstable patients, the option of ventilation for several (6 to 8) hours with normobaric oxygen should be considered. Under these conditions the risk of pulmonary oxygen toxicity is negligible and the risk of cerebral oxygen toxicity is non-existent. Animal model experiments, as well as controlled prospective clinical studies are required to determine the effectiveness of the proposed treatment.

Massive air embolism is a rare event in cardiac surgery with cardiopulmonary bypass (CPB). A survey of 349 surgeons covering 374,819 operations using a pump oxygenator showed that arterial line air embolism occurred in 429 patients[1], i.e. once per 1,000 procedures. These accidents caused permanent injury in 61 patients and 92 deaths. In a comment on this survey, Peirce[2] emphasized that the specific therapy for arterial air embolism is hyperbaric oxygen (HBO). He suggested that the reason for the infrequent reports of hyperbaric treatment in such circumstances was the lack of preparedness on the part of most thoracic surgeons to deal with this treatable emergency. Moreover, many surgeons believe that lesions due to arterial air embolism are self limited and this gives rise to an attitude of fatalism and inaction. In view of the availability of modern, fully equipped hyperbaric chambers in a large number of medical centers, this is a mistaken attitude. As a result many patients may develop neurological sequelae which could have been prevented and may even be denied life saving treatment.

We have recently stressed that, on the slightest suspicion of air embolism during CPB, the patient should be treated with HBO as quickly as possible, even before the appearance of any neurologic manifestation of cerebral ischemia[3]. Neurologists are frequently called in by cardiac surgeons to assess the acute neurologic deficits which appear in cases of overt cerebral embolism during CPB. They also evaluate large numbers of patients complaining of minimal neurologic and neuropsychological dysfunction after apparently uncomplicated cardiac surgery with CPB. There has recently been renewed discussion of these subtle, long-term neurological complications of open heart surgery in an editorial in the Annals of Neurology[4]. However, as yet no possible therapeutic approach has been proposed. We now summarize studies demonstrating that microbubble embolism does occur during CPB. In view of the possibility that these microbubbles are responsible for the long-term neurologic deficits after CPB, we suggest active treatment with oxygen immediately after the completion of surgery.

Cardiac surgery and microbubbles

While massive air embolism is fortunately rare, a growing body of data suggests that microbubble embolism is common during cardiac surgery with CPB. Modern technology has made it possible for us to take a closer look at the arterial circulation and to demonstrate that microbubble embolism does indeed occur during CPB. Topol et al.[5], using transesophageal two-dimensional echocardiography, detected microbubbles in the left ventricle in 41% of patients undergoing cardiac operations[6]. As expected, microbubbles were more common during valvular or other intracardiac manipulations than in coronary revascularization. The authors emphasized that when grade 2 (10-25 bubbles per frame) or grade 3 microbubbles (too many to count) were identified, mechanical attempts to eradicate them were unsuccessful. Since it was found that microbubbles are not predictive of post-operative neurologic complications, the authors concluded that attempts to eradicate them are unnecessary. They suggested that air bubbles up to 100μ may be cleared from the circulation without any loss of perfusion, which would explain the fact that no stroke or new focal deficit was detected. However, there was no long-term neurologic follow-up as part of this study nor did the study include any neuropsychological tests. Rodigas et al.[6] had previously detected microbubbles in 62% of patients undergoing cardiac surgery.

While it is evident that microbubbles are very common in the heart, the cerebral circulation also merits close investigation. Microbubbles have been found here too by means of the same technology. Gaseous microemboli were detected by Padayachee et al. in the middle cerebral artery by transcranial pulsed Doppler ultrasound during the insertion of the aortic cannula in 22 of 27 patients[7]. In a further study the same authors reported that filtration of the arterial blood during CPB significantly reduced gaseous microemboli detected in the middle cerebral artery[8]. Using the same technology, van der Linden and Casimir-Ahn[9] detected cerebral air embolism in 10 of 10 patients during open-heart valve operations despite careful de-airing procedures. Particularly large numbers of emboli were detected during the filling of the empty beating heart.

CPB and subtle-neurologic damage

Cardiac surgery has reached the stage where mortality and even gross morbidity are low. Although the frequency of overt cerebral complications during CPB has decreased with the refinement of operative techniques, the subtle cerebral damage caused by microemboli seems to be an integral part of operative cardiac procedures.

In an early study, Gilman[10] reported cerebral disturbances in 34% of patients (12 out of 34) who had undergone open heart surgery. Heller et al.[11] described the psychiatric complications of open-heart surgery which between 1965 and 1969, declined from 38% to 24%. In a prospective study of 227 patients undergoing heart surgery[12], Savageau et al. performed neuropsychological tests before and after the operation. The mean group performance deteriorated in all components of the test. On the ninth post-operative day only 70% of the patients performed within one standard deviation of their preoperative score. However, in this study no comparison was made with a control group.

In another prospective study of 312 patients undergoing elective coronary artery bypass surgery[12], neurologic complications were found in 61% of the patients. One patient died as a result of neurologic disorders and 4 patients (1.3%) had severe disability. Forty-eight patients (15%) were mildly disabled during the early post-operative period. Since in most cases the operations were routine and uncomplicated, the authors deduced that many neurologic disorders result from hazards inherent in the extracorporeal circulation process. In a further study the same authors compared these results with those of a control group of 50 patients who underwent major vascular surgery without CPB[14]. CNS complications were more frequent and severe after cardiac surgery using CPB than after major surgical procedures in which CPB was not employed.

In a controlled prospective study, Smith et al.[15] compared 55 patients undergoing coronary artery surgery with 20 patients having thoracic or major vascular surgery. Major persisting neurologic changes were rare but minor abnormalities were significantly more common in the former group of patients. The severity of the impairment correlated with the duration of the bypass procedure. An association between the microemboli generated by bubble oxygenators during CPB and brain injury was suggested earlier by Brennan et al.[16] as a result of experiments conducted using a canine model of CPB.

In the search for an objective index of brain dysfunction, Henriksen[17] used single photon emission computerized tomography (SPECT) in 37 patients before and after heart surgery. Cerebral blood flow fell globally and was still found to be reduced up to a year later. Computerized tomography (CT) was used by Muraoka et al.[18] to assess brain morphology following cardiac operations with CPB maintained by a bubble oxygenator having a 40μ filter. Post-operative CT showed a decreased brain mass which recovered within 6 months. The authors speculated that microbubbles may have been responsible for these changes.

In another study[19], Blauth et al. used fluorescein angiography to demonstrate focal leakage of fluorescein in 3 patients undergoing coronary artery surgery. As the blood-retina barrier is analogous to the blood-brain barrier, this leakage may reflect a similar process in the cerebral circulation. In a further study[20], 21 patients undergoing elective coronary operations were subjected to retinal fluorescein angiography 5 minutes before CPB was terminated. All 21 patients had retinal microvascular occlusions indicative of microembolism.

In a recent controlled study combining human pathology and an animal model, Moody et al. examined the brains of patients who had died after surgery with or without CPB[21]. Many focal dilatations or very small aneurysms were observed in the terminal arterioles and capillaries in 4 of 5 patients and 6 dogs that had undergone CPB. There were no such observations in the group of 34 patients and 6 dogs that had not undergone CPB. Most of the dilatations appeared to be empty and so were probably the sites of gas bubbles or fat emboli. The authors suggested that this might be the anatomic correlate of the neurologic deficit and intellectual dysfunction seen in a considerable percentage of patients after CPB.

In an editorial in the Annals of Neurology, Gilman[4] commented on the study by Moody et al. and summarized other studies demonstrating the surprisingly high incidence of long-term neurologic impairment post-CPB in heart surgery. He emphasized that while the exact cause of many of the neurologic complications of open-heart surgery has not yet been established, mounting evidence points to ischemic events secondary to microemboli.

However, despite the suggestion in all of the above mentioned studies that microbubble emboli may indeed be responsible for cerebral deficits following CPB, no therapeutic approach has been proposed.

Microbubbles and Decompression Sickness (DCS)

Decompression sickness affecting scuba divers is another clinical situation in which arterialized bubbles may cause injury to the central nervous system[22]. Although the exact pathophysiology of spinal DCS is still controversial[23], overt cerebral manifestations in a scuba diver as a consequence of arterial air bubbles may be the result of DCS alone or DCS in combination with pulmonary barotrauma air embolism[22,24].

In contrast, silent (asymptomatic) microbubbles, i.e., nitrogen bubbles released into the venous circulation but which do not produce any clinical signs or symptoms, are relatively common on ascent from compressed air diving[25,26]. As mammalian lungs are competent filters for microbubbles larger than 20μ, it is assumed that bubbles smaller than this are harmless because they will pass through the cerebral circulation. To assess the effect of microbubbles on the brain, Hills and James[27] used guinea pigs in an animal model. They injected 15±5 μ diameter microbubbles in 5 mL of plasma into the animal's carotid artery. All of the animals demonstrated extravasation of trypan blue, evidence of blood-brain barrier dysfunction. This study supported the contention that unrecognized silent bubbles may cause subtle, chronic neurologic damage in divers.

In fact, neuropathological examination of the spinal cords and brains of divers who died accidentally has revealed chronic degenerative changes not related to the cause of death[28,29]. These unrecognized, asymptomatic changes may be ascribed at least partially to intravascular bubble formation.

As in CPB, retinal fluorescein angiography and SPECT have been used to investigate possible retinal or brain abnormalities in divers. Retinal fluorescein angiography of the ocular fundi in divers with no visual symptoms revealed changes consistent with obstruction of the retinal and choroidal circulation[30]. Intravascular bubble formation during decompression, or other vascular or blood factors related to hyperbaric conditions per se, were postulated as the cause of the reported microvascular occlusion.

Cerebral perfusion deficits as measured by SPECT were demonstrated in all 23 cases of neurological DCS examined[31]. Even in cases with classic spinal cord presentation, SPECT showed clear cerebral perfusion deficits due most probably to unrecognized silent microbubbles.

The well documented association between interatrial shunts and decompression sickness in divers[32,33] emphasizes the pathophysiological impact of microbubbles on the central nervous system. In the diver these are preventable by carefully designed diving profiles and in the case of neurological DCS the specific treatment is HBO as soon as possible.

Summary and suggested management

While massive air embolism during cardiac surgery is a rare event, microbubbles seem to be an inherent side effect of CPB. Surgeons have reached the mistaken conclusion that, since patients recover from the operation and are discharged from hospital, these microbubbles must be harmless. In fact, a considerable number of patients suffer some kind of neurologic deficit. This does not involve basic motor skills but is rather an impairment of higher functions. Personality changes and intellectual deterioration, though not affecting basic skills, may have a profound effect on the patient's quality of life and capacity for work after the operation. At this stage the neurologist has no specific therapy to offer. Even so, if these neu-

rological sequelae are indeed due to air microbubble embolism during CPB, the question remains as to the measures which might be taken to prevent them.

Contemporary CPB technology does not seem to offer a reasonable solution which will totally eliminate microbubble emboli. Until a new technology is developed we must treat this embolism aggressively. Since the specific treatment for air embolism is HBO, whatever the etiology, this mode of therapy may also be applicable to microbubbles. HBO is considered a specific therapy for air embolism because it is based on the mechanical compression of air bubbles according to Boyle's law: the volume of a gas is inversely proportional to the pressure to which it is subjected. At the same time, hyperbaric oxygen reduces the partial pressure of nitrogen in the blood, increasing the gradient between the bubbles and the blood and accelerating bubble resorption (the "oxygen window"). HBO also increases ischemic tissue oxygenation and may reduce brain edema[2]. The administration of hyperbaric oxygen does not necessarily require a large multiplace chamber providing all the facilities available in a postoperative unit. Air embolism complicating open-heart surgery was treated successfully in a monoplace chamber as long ago as 1974[34]. The requirements for chest tubes, respiratory support and careful hemodynamic and acid-base monitoring are all met by modern monoplace chambers.

Normobaric oxygen, by widening the "oxygen window", will also enhance the rate at which air bubbles are resolved and eliminated from nervous and other tissues. Thus immediate postoperative ventilation for several (6 to 8) hours with normobaric oxygen will be preferable to air ventilation and may be sufficient to prevent neurologic deficits after CPB in many cases. Under these conditions the risk of pulmonary oxygen toxicity is minimal. Significant changes in vital capacity while breathing normobaric oxygen are detected only after 24 hours of continuous O_2 exposure[35]. Clark and Lambertsen[36] found a 2% reduction in vital capacity after 10 hours breathing normobaric oxygen. It would therefore appear that normobaric oxygen is safe when breathed for several (6 to 8) hours and it is also very easily administered.

Animal model experiments and controlled prospective clinical studies are required to determine the potential role of oxygen in post-cardiac surgery patients.

References

1. Stoney WS, Alford WC Jr, Burrus GR, et al. Air embolism and other accidents using pump oxygenators. *Ann Thorac Surg* 1980;29:336-340.
2. Peirce EC II. Specific therapy for arterial air embolism. *Ann Thorac Surg* 1980;29:300-303.
3. Kol S, Ammar R, Weisz C, Melamed Y. Hyperbaric oxygenation for arterial air embolism during cardiopulmonary bypass. *Ann Thorac Surg* 1993;55:401-403.
4. Gilman S. Neurological complications of open heart surgery. *Ann Neurol* 1990 28:475-476.
5. Topol EJ, Humphrey LS, Borkon AM, et al. Value of intraoperative left ventricular microbubbles detected by transesophageal two-dimensional echocardiography in predicting neurologic outcome after cardiac operations. *Am J Cardiol* 1985;56:773-775.
6. Rodigas PC, Meyer FJ, Haasler GB, et al. Intraoperative 2-dimensional echocardiography: ejection of microbubbles from the left ventricle after cardiac surgery. *Am J Cardiol* 1982;50:1130-1132.
7. Padayachee TS, Parsons S, Theobold R, et al. The detection of microemboli in the middle cerebral artery during cardiopulmonary bypass: a transcranial Doppler ultrasound investigation using membrane and bubble oxygenators. *Ann Thorac Surg* 1987;44:298-302.
8. Padayachee TS, Parsons S, Theobold R, et al. The effect of arterial filtration on reduction of gaseous microemboli in the middle cerebral artery during cardiopulmonary bypass. *Ann Thorac Surg* 1988;45:647-649.
9. van der Linden J, Casimir-Ahn H. When do cerebral emboli appear during open heart operations? A transcranial Doppler study. *Ann Thorac Surg* 1991;51:237-241.
10. Gilman S. Cerebral disorders after open-heart operations. *N Engl J Med* 1965;272:489-498.
11. Heller SS, Frank KA, Malm JR, et al. Psychiatric complications of open-heart surgery. A re-examination. *N Engl J Med* 1970;283:1015-1020.
12. Savageau JA, Stanton BA, Jenkins CD, Klein MD. Neuropsychological dysfunction following elective cardiac operation. I. Early assessment. *J Thorac Cardiovasc Surg* 1982;84:585-594.
13. Shaw PJ, Bates D, Cartlidge NE, et al. Early neurological complications of coronary artery bypass surgery. *Br Med J* 1985;291:1384-1387.
14. Shaw PJ, Bates D, Cartlidge NE, et al. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 1987;18:700-707.
15. Smith PL, Treasure T, Newman SP, et al. Cerebral consequences of cardiopulmonary bypass. *Lancet* 1986;1: 823-825.
16. Brennan RW, Patterson RH Jr, Kessler J. Cerebral blood flow and metabolism during cardiopulmonary bypass; evidence of microembolic encephalopathy. *Neurology* 1971; 21:665-672.
17. Henriksen L. Evidence suggestive of diffuse brain damage following cardiac operations. *Lancet* 1984;1:816-820.
18. Muraoka R, Yokota M, Aoshima M, et al. Subclinical changes in brain morphology following cardiac operations as reflected by computed tomographic scans of the brain. *J Thorac Cardiovasc Surg* 1981;81:364-369.
19. Blauth C, Arnold J, Kohner EM, Taylor KM. Retinal microembolism during cardiopulmonary bypass demonstrated by fluorescein angiography. *Lancet* 1986;2: 837-839.
20. Blauth C, Arnold J, Schulenberg WE, et al. Cerebral microembolism during cardiopulmonary bypass. Retinal microvascular studies in vivo with fluorescein angiography. *J Thorac Cardiovasc Surg* 1988;95:668-676.
21. Moody DM, Bell MA, Challa VR, et al. Brain microemboli during cardiac surgery or aortography. *Ann Neurol* 1990; 28:477-486.
22. Melamed Y, Shupak A, Bitterman H. Medical problems associated with underwater diving. *N Engl J Med* 1992; 326:30-35.
23. Aharon-Peretz J, Adir Y, Gordon CR, et al. Spinal cord decompression sickness in sport diving. *Arch Neurol* 1993;50:753-756.
24. Dick APK, Massey EW. Neurologic presentation of decompression sickness and air embolism in sport divers. *Neurology* 1985;35:667-671.
25. Evans A, Barnard EEP, Walder DN. Detection of gas bubbles in man at decompression. *Aerosp Med* 1972;43: 1095-1096.
26. Spencer MP, Campbell SD. Development of bubbles in venous and arterial blood during hyperbaric decompression. *Bull Mason Clin* 1968;22:26-32.
27. Hills BA, James PB. Microbubble damage to the bloodbrain barrier: relevance to decompression sickness. *Undersea Biomed Res* 1991;18:111-116.
28. Palmer AC, Calder IM, Hughes JT. Spinal corddegeneration in divers. *Lancet* 1987;2:1365-1366.
29. Palmer AC, Calder IM, Yates PO. Cerebral vasculopathy in divers. In: Sterk W, Geeraedts L, eds. *Proceedings of the XVI annual meeting of the European Undersea Biomedical Society.* Amsterdam: Foundation for Hyperbaric Medicine, 1990:137-144.
30. Polkinghorne PJ, Sehmi K, Cross MR, et al. Ocular fundus lesions in divers. *Lancet* 1988;2:1381-1383.
31. Adkisson GH, MacLeod MA, Hodgson M, et al. Cerebral perfusion deficits in dysbaric illness. *Lancet* 1989;2: 119-122.
32. Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. *Lancet* 1989jl: 513-514.
33. Wilmshurst PT, Byrne JC, Webb-Peploe MM. Relation between interatrial shunts and decompression sickness in divers. *Lancet* 1989;2:1302-1306.
34. Hart GB. Treatment of decompression illness and air embolism with hyperbaric oxygen. *Aerosp Med* 1974;45: 1190-1193.
35. Comroe JH Jr, Dripps RD, Dumke PR, Deming M. Oxygen toxicity. The effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. *JAMA* 1945;128:710-717.
36. Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. *Pharmacol Rev* 1971;23:37-133.

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Clostridium difficile Bacteremia in an Intravenous Drug User With HIV Infection

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Abstract

Clostridium difficile is a common isolate from the skin and the hospital environment and is a frequent cause of antibiotic associated diarrhea and colitis. HIV infected patients are frequently treated with multiple antibiotics and are at high risk of colonization and infection with this organism. Documented bacteremia with *C. difficile* is uncommon despite the frequent infection of critically ill patients with this organism. We report a case of *C. difficile* bacteremia with the sepsis syndrome and multiorgan failure in an HIV infected patient. Altered immune function from HIV infection is likely to have contributed to the bacteremia in this case.

Key Words: Clostridium difficile; Adult Respiratory Distress Syndrome (ARDS); Sepsis

Clostridium difficile is a gram-positive, spore forming bacterium. It is the principal etiologic agent of antibiotic associated colitis [1]. Other less common sites of infection that have been reported include the skin [1,2], bone [1-3], the male and female genito-urinary tracts [1,5], spleen [4], peritoneum [1,5] and pleura [5]. Bacteremia has been described only rarely [1,5-8]. We report a