Iatrogenic cerebral gas embolism: analysis of the presentation, management and outcomes of patients referred to The Alfred Hospital Hyperbaric Unit

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Abstract

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Introduction: The aim of this study was to review patients with iatrogenic cerebral gas embolism (CGE) referred to The Alfred Hospital hyperbaric unit to determine whether hyperbaric oxygen treatment (HBOT) reduced morbidity and mortality.

Methods: This is a retrospective cohort study with a contemporaneous comparison group of patients referred between January 1998 and December 2014. The primary end point was good neurological outcome at the time of discharge from hospital or rehabilitation facility as assessed by the Glasgow Outcome Scale (GOS-E).

Results: Thirty-six patients were treated with HBOT for CGE and nine patients were diagnosed with CGE but did not receive HBOT. Thirty-two patients developed CGE from an arterial source and 13 from a venous source. The mean time from recognition of the event to institution of HBOT was 15 hours. Four of 45 patients (8.9%) died. Good neurological outcomes (defined as GOS-E 7 or 8) occurred in 27 patients and moderate disability in 13. The only independent factor that was associated with good neurological outcome was time to first HBOT (OR 0.94, 0.89–0.99; $P = 0.05$). Hemiplegia as the first presenting sign, however, was associated with poor outcome (OR 0.27, 0.06–1.08; $P = 0.05$). The source of embolus (arterial versus venous), hyperbaric treatment table used and patient age did not affect outcome.

Conclusion: Appropriate treatment of CGE with hyperbaric oxygen was found to be impeded by delays in diagnosis and subsequent transfer of patients. Better neurological outcome was associated with HBOT within eight hours of CGE.

Key words

Cerebral arterial gas embolism (CAGE); venous gas embolism; hyperbaric oxygen therapy; outcome; clinical audit

Introduction

Iatrogenic venous gas embolism (VGE) and arterial gas embolism (AGE) can occur as a result of many hospital-related procedures. This complication has been reported in almost all areas of clinical and surgical practice including cardiopulmonary bypass surgery,[1,2] angiography,[3] laparoscopy,[4] neurosurgery, caesarian delivery,[5] irrigation with hydrogen peroxide,[6] mechanical ventilation, central venous catheter placement and haemodialysis.[7] In most cases the embolised gas is air, but other medical gases such as helium[8] and carbon dioxide[9] have been described. AGE can occur as a result of direct injection into the arterial system or if there is cross-over from the venous system. VGE can move from the venous into the arterial system (paradoxical air embolism) through a right-to-left intra-cardiac shunt (persistent foramen ovale), through the pulmonary vasculature[10] or as a result of barotrauma. Bothma recently described a third generic mechanism called retrograde cerebral venous gas embolism (CVGE). This process depends on flow dynamics, buoyancy, bubble size and patient positioning.[11,12] Cerebral gas embolism (CGE) is a general term used in this article to encompass all three of these phenomena.

The pathophysiology of gas embolism is complex. Small-sized bubbles that enter either the venous or arterial circulation have both mechanical and inflammatory consequences. Gas bubbles that enter the venous system can make their way into the pulmonary circulation and impair right ventricular function. Furthermore, they can cross into the arterial circulation in the presence of an atrial or ventricular septal defect. Gas bubbles which enter the arterial circulation eventually lodge in small vessels and obstruct flow of oxygenated blood to cells causing end-organ ischaemia and endothelial injury with subsequent cell oedema and death. When gas lodges in coronary and cerebral arterioles, it can have devastating effects such as myocardial infarction, dysrhythmias, seizures and stroke phenomena. Imaging modalities, including CT and MRI scanning, may support a diagnosis but are not particularly sensitive. There is no relationship between volume of embolised gas and severity of symptoms.[13]

Furthermore, these ischaemic and local inflammatory processes activate leucocytes, platelets, complement and the clotting cascade which can result in endothelial injury and thrombus formation. Granulocyte-mediated reperfusion injuries may also occur.

In accordance with Boyle's law, hyperbaric oxygen (HBO) reduces the volume of the gas bubbles in the vessel so that blood flow can be re-established. Exposing the bubbles to hyperbaric oxygen accelerates denitrogenation by creating a gradient between the partial pressure of nitrogen in the gas bubbles and the blood (Henry's Law). This results in rapid reabsorption of nitrogen back into the blood with subsequent reduction and removal of air emboli. Therefore, in the case

of CGE, the potential benefits of HBO are thought to be reduction in the size of the penumbra and ischaemic insult, reduction in cerebral oedema by limiting cerebral vascular permeability, reduction in intracranial pressure due to oxygen-driven cerebral vasoconstriction and, finally, limiting endothelial injury by ameliorating leucocyte activation and adherence.[13–17]

Hyperbaric oxygen treatment (HBOT) is the standard treatment for diving-related decompression sickness (DCS) and gas embolism; however, there are currently no randomised controlled trials to guide best practice. Using standardised HBOT tables, recompression promotes the most rapid and complete removal of gas bubbles and, therefore, should enhance neurological outcome. Based on the pathophysiology of gas embolism, the earliest possible commencement of HBOT would seem optimal to prevent neurological sequelae by reducing ischaemic time. The efficacy of HBOT in this setting has been validated by extensive clinical experience and scientific studies.[18]

In contrast, there are few series describing iatrogenic CGE and even fewer guidelines regarding the optimal hyperbaric management. This is partly due to its infrequent occurrence. To date, most Australian literature pertains to scuba diving-related CGE, with the Prince of Wales hyperbaric unit reporting 26 cases that presented over a decade.[19] The intention of our study was to focus on presentation, management and outcome patterns of non-diving-related venous and arterial cerebral gas embolism that occurred as a result of medical procedures and were subsequently referred to The Alfred Hyperbaric Unit in Melbourne.

Methods

PATIENT SELECTION

This was a retrospective cohort study with a contemporaneous comparison group. The study examined patients admitted to the Alfred Hospital with a diagnosis of CGE between 01 January 1998 and 31 December 2014. The research proposal was approved by the Alfred Ethics Committee (AH 55/14). Using the established database at the Alfred Hyperbaric Unit, all patients were sought who had been referred to the unit from within The Alfred or from other peripheral hospitals following witnessed or suspected gas embolism. A search of The Alfred Hospital clinical coding system for air embolism (ICD9 958.0 and ICD-10 code T79.0), and air emboli from infusion, transfusion, therapeutic injection (ICD 9 999.1 and ICD-10 T80) was then performed. This provided an indication of the capture rate of all patients with air emboli during the study period and also generated a comparator group totalling nine patients who did not receive HBOT. Gas embolism was confirmed if the clinical notes reported visible gas, cardiovascular and/or central nervous system instability in the setting of an invasive procedure or if gas was visualised on CT or MRI. Exclusion criteria included patients in whom the aetiology was likely to be mixed gaseous or thromboembolic, patients in whom hyperbaric treatment could not be completed owing to cardiovascular instability and patients with CGE as a result of scuba diving.

Further examination of the hyperbaric unit's database revealed the number of treatments administered, the treatment tables used and whether other ancillary treatments were instituted, such as a lignocaine infusion. Individual medical records were then scrutinized for details pertaining to basic patient demographics, the nature of the initiating iatrogenic insult, time delay to presentation and eventual neurological outcome.

NEUROLOGICAL OUTCOME

An assessment of neurological outcome was made after the first hyperbaric treatment and at hospital discharge using the Extended Glasgow Outcome Scale (GOS-E) structured questionnaire.[20,21] The GOS-E is a practical index of social and functional outcome following head injury designed to complement the Glasgow Coma Scale (GCS) as the basis of a predictive system. Patients are assigned to one of five possible outcome categories: death, persistent vegetative state, severe disability, moderate disability, and good outcome. Using the GOS-E, each of the three categories applicable to conscious patients are subdivided into upper and lower bands that results in eight possible categories. A good neurological outcome was defined as a GOS-E of 7 or 8 (independent). The secondary outcomes included relationship between eventual neurological status and timing of hyperbaric treatment, recompression table used and the total number of treatments administered.

STATISTICS

Parametric data are presented as mean (SD), non-parametric as median (IQR), and categorical as proportions. A two sample *t*-test was used to compare the ages and weights of the HBOT and non-HBOT groups. The Pearson chi squared test was used to establish if there was an association between the confounders (gender, admission source, site of CGE, aetiology of CGE), the outcomes (mortality and complications) and predictors (HBOT versus no HBOT). Multivariate logistic regression was used for all independent variables found to be associated with mortality on univariate logistic regression with a two-tailed significance set at a P-value < 0.05. Results were expressed as odds ratio (OR) with 95% confidence intervals (CI). Data from patients with missing values were not analysed.

Results

Over the 17-year period, 61 patients were identified with an initial diagnosis of a CGE using the ICD search. A total of 36 patients were treated by the Alfred Hyperbaric Service

Table 1

Demographics of patients with cerebral gas embolism; good neurological outcome was defined as Glasgow Outcome Scale (GOS-E) 7 or 8; * $P = 0.01$; all other factors not significant; CVAD – central venous access device; $ETCO_2$ – end-tidal carbon dioxide; CVA – cerebrovascular accident

	Neurological outcome	
	Good (n = 27)	**Poor (n = 18)**
Patients		
Age (mean, 95% CI)	56.2 (44.9–63.6)	56.4 (48.4–65.7)
Gender (M:F)	16:11	9:9
Referral base		
Inpatient	19	10
Other hospital	8	8
Predisposing factors		
Cardiac surgery	16	8
Other surgery	4	0
Trauma	2	3
Interventional radiology	3	1
CVAD	2	6
Source		
Arterial	20	12
Venous	7	6
Presenting symptoms		
ET CO_2	4	0
Observed embolus	12	6
Seizure	2	1
Blindness	2	2
CVA*	2	7
Arrhythmia	2	1
Cardiac arrest	2	0
Respiratory arrest	1	1

Table 2

Interventions instituted after diagnosis of iatrogenic cerebral gas embolism; good neurological outcome was defined as Glasgow Outcome Scale (GOS-E) of 7 or 8; * $P = 0.05$; † $P = 0.002$ CT – computerised tomography; MRI – magnetic resonance imaging; HBOT – hyperbaric oxygen treatment, including RN 62 – Royal Navy treatment table 62; RN 61 – Royal Navy treatment table 61; 18:90:30 – a 284 kPa treatment table and Comex 30 – 406 kPa treatment table using a helium/oxygen mix (HeO_2)

	Neurological outcome	
	Good (n = 27)	**Poor (n = 18)**
Imaging		
CT	9	11
MRI	2	3
Both CT and MRI	3	1
Nil	13	3
Ancillary therapy		
Trendelenburg	5	0
Lignocaine	9	5
Prednisolone	2	0
Nil	16	13
Hyperbaric oxygen		
Time to HBOT (h)*	8.8 (4.7–12.8)	16.5 (9.0–24.1)
Treatments† (median, range)	1 (0.8–1.5)	3 (1.7–4.2)
RN 62	5	7
RN 61	13	7
18:90:30	2	1
Comex	1	0

and 25 did not receive HBOT. The authors reviewed the medical records of these 25 patients and determined that 16 patients had received the wrong ICD code and the other nine had been correctly diagnosed with CGE but not referred to the hyperbaric unit.

Table 1 details the characteristics of the cohort. The source of embolus was arterial in 32 patients and venous in 13 patients. The overall mortality was four of 45 patients (8.7%) (three treated with HBOT and one in the non-treated group). The most common precipitating events were cardiac surgery (24 patients) or manipulation of central venous access devices (eight patients). The most frequent presenting signs were non-haemorrhagic hemiplegia on awakening from cardiac surgery (nine patients), cardiac arrest (two patients) or respiratory arrest (two patients). An air embolus was witnessed in the cardiopulmonary bypass circuit in 18 patients and four had presumed CGE with sudden loss of their end-tidal capnography trace.

Apart from standard resuscitation drugs, 14 patients received lignocaine infusions, two received steroids and five were placed in Trendelenburg positioning. Diagnostic imaging was performed in 29 patients (20 patients had CT, five patients had MRI, four had both CT and MRI) and 16 patients had no scanning (Table 2). HBOT was offered to 36 patients. The tables frequently used were the Royal Navy Treatment Table 62 (RN 62), RN 61, an 18 msw (284 kPa) treatment table and a Comex 30 (405 kPa). The initial treatment table selected varied depending on the source of embolus, the time delay to treatment and the neurological deficit observed.

Of the patients who did receive HBOT, the majority were male, were usually younger (52.5, IQR 31–75 years old versus 64.0, IQR 29–67) and had witnessed events. The mean time from recognition of CGE to institution of HBOT was 15.0 (12.9) hours with no significant difference between the Alfred patients and those referred from other hospitals (16 (12.3) h vs. 12.8 (13.7) h; $P = 0.47$). Twenty-nine patients were referred from within the Alfred and 16 were transferred from another hospital.

The GOS-E of 30 patients could not be assessed at the end of the first HBOT as they were still sedated or intubated. The mean GOS-E at discharge was 6.5 (2.1). Good neurological outcomes (defined as GOS-E 7 or 8) occurred in 27 patients,

Table 3
Univariate regression analysis of factors associated with favourable neurological outcome; * $P = 0.05$; CAGE – cerebral arterial gas embolism; CVA – cerebral vascular accident; CVGE – cerebral venous gas embolism; HBOT – hyperbaric oxygen treatment, including RN 62 – Royal Navy treatment table 62. For factors with a binary outcome (cardiac surgery, CVGE, CAGE, HBOT) the odds ratio represents the presence or absence of the factor; for continuous data the estimate is the odds ratio for a unit increase for the factor (e.g., per year).

	Odds ratio	Std error	95% CI
Patient factors			
Age	0.99	0.01	0.96–1.02
Transfer	2.18	1.48	0.54–8.76
Aetiology			
CAGE:CVGE	1.16	0.20	0.25–5.33
Cardiac surgery	2.28	2.01	0.68–2.51
Presentation			
CVA	0.27	0.19	0.06–1.08
Cardiac	4.38	5.05	0.45–42.1
Hyperbaric oxygen			
HBOT:no HBOT	0.47	0.42	0.08–2.71
Time to first HBOT*	0.94	0.03	0.89–0.99
Early HBOT (< 8hrs)	3.25	2.30	0.81–13.03
Late HBOT (> 24hrs)	0.27	0.20	0.06–1.14
RN 62:Other table	0.46	0.32	0.11–1.83

20 in the HBOT group and seven in the non-HBOT group. Patients with good neurological outcome were treated with HBOT earlier (8.8 (1.9) hours vs. 16.5 (3.6) h; $P = 0.05$), received fewer treatments (1, IQR 1–2) vs. 1.5, IQR 1–5; $P = 0.002$) and were mainly treated with a shorter table (13 RN 61 and five RN 62 vs. seven RN 61and seven RN 62). The association between the number of HBOT and outcome was influenced by the clinicians involved. Prompt resolution of symptoms was associated with one or two HBOT treatments. In contrast, incomplete resolution after the first treatment initiated further treatment until lack of ongoing improvement or stable persistent neurological impairment.

Table 3 summarises the univariate analysis for the 11 variables considered. On univariate analysis the only independent factor associated with good neurological outcome was time to first HBOT treatment (OR 0.94, 0.89–0.99; $P = 0.05$). Those patients with poor neurological outcome were more often referred from other hospitals (8 of 18 vs. 10 of 27), had a CVAD as the source of embolus (6 of 18 vs 2 of 27) and had longer delays to initial treatment (16.5 (3.6) h vs. 8.8 (1.9) h; $P = 0.05$). Hemiplegia, as the first presenting sign, was associated with poor outcome (OR 0.2, 0.06–1.08; $P = 0.05$). No association between outcome and cardiac surgery (OR 0.99, 0.96–1.02; $P = 0.54$) or arterial source of CGE (OR 1.32, 0.36–4.81; $P = 0.36$) could be established. Although patients who were transferred had poorer neurological outcomes, there were some who had complete recovery.

Discussion

This is the largest Australian retrospective case series of iatrogenic gas embolism to date. It includes 45 cases of both arterial and venous gas embolism over a 17-year period. Whilst the incidence of CGE in this series was low, it was comparable to the incidence reported by Bessereau of a confirmed CGE rate of 2.65 per 100,000 hospital admissions.[22]

The obvious interpretation of our series is that there are a number of preventable measures which could impact on recovery from CGE. In particular earlier recognition, greater compliance with gas embolism treatment protocols and earlier referral to a hyperbaric unit are recommended.[23,24] Despite the presence of a hyperbaric medical unit on site, the mortality rate was 8.7% and complete neurological recovery only occurred in 27 of the 45 cases.

The effects of gas embolism on cerebral blood flow and subsequent ischaemia have been demonstrated by a number of authors.[25–27] The need for urgent definitive treatment has also been stressed by many.[13,19,28] Most authors agree that early HBOT treatment (certainly within eight hours) is associated with improved outcome.[22,28–30] In this series, early institution of HBOT was associated with better neurological outcome. Previous reports suggest that the diagnosis of CGE is often not made in cardiothoracic surgery until post-bypass stroke has occurred. Delayed presentation does not preclude HBOT and this series demonstrated significant improvement is possible even when hyperbaric treatment is more than 24 hours post insult.[2,32] In reality, delays inevitably occur if the patient is transferred from another hospital. This makes treatment within the optimal time frame difficult to achieve.

One retrospective study reported a good recovery in 80% of patients when HBOT was carried out within three hours, and only 48% if the delay exceeded three hours.[28,30] HBOT after a significant delay should still be considered, as some case reports suggest good neurological outcome is possible.[32,33] In one case where there was sudden onset of unresponsiveness followed by seizure activity during a diagnostic bronchoscopy, the clinical diagnosis was unclear and HBOT was not instituted until 52 hours after the initiating event, followed by two additional HBOT sessions and the patient made a full neurological recovery.[32]

Currently a number of HBOT regimes exist. The choice of HBOT table depends on multiple factors. For example the decision can be based on whether the patient with CGE is referred in the acute phase (less than eight hours after the event) or the delayed phase (greater than 24 hours after the event). In other published series, the choice of treatment table is driven by the cause of the CGE (Table 4).

Traditionally CGE related to scuba diving was treated with a US Navy Treatment Table 6A, which involves a 30-minute

Table 4

Previous case series of ≥ 10 patients with cerebral gas embolism with details of treatment tables, delay to therapy and outcome
CAGE – cerebral arterial gas embolism; CNS – central nervous system; CVC – central venous catheter; CVGE – cerebral venous gas embolism; HBOT – hyperbaric oxygen treatment; RN 62 – Royal Navy treatment table 62; USN 6 – United States Navy treatment table 6; VAE – venous air embolism; other hyperbaric treatment tables specific to the treating unit with maximum pressures of 304, 406 and 608 kPa.

Author	Patients	HBOT table	Delay to treatment (h)	Neurological outcome	Mortality	Comments
Boussuges[30]	113	608 kPa with neurology; 203 kPa without	Not recorded	69% (78) recovery	6 (5%)	71% (80) venous origin (CVC or dialysis)
Bacha[34]	Not reported	608 kPa then 304 kPa	< 12	21% sequelae	14%	Lower mortality with < 12 h delay to treatment
Ziser[35]	17	USN 6A	9.6 (mean)	8 recovery	3	Good outcome if Rx< 4 h
Blanc[28]	86	608 kPa 10 min then 203 kPa 60 min	3–8	58% (50) recovery	7	63 CVGE
Benson[36]	19	USN 6A or USN 6	8.9 (mean)	5 resolved 11 improved	5	9 CVGE
Trytko[19]	26	280 kPa	Divers 2–44; Non divers 0.75–14	2 severely affected	0	18 diving-related
Bessereau[22]	125	406 kPa then 253 kPa then 203 kPa	6 (mean)	43% (54) CNS sequelae	15 (12%)	32% (40) CVGE
Gibson[2]	12	RN 62	18 (4–48)	1 CNS sequelae	1	6 treated > 24 h post event
Tekle[29]	36	USN 6	19 patients < 6	26 "*favourable*"	1	24 VAE

period at 609 kPa breathing air. This deep air spike was designed to rapidly compress bubbles.[37] Most clinical and animal studies, however, have found no objective advantage in starting recompression at levels greater than 2.8 ATA.[15,37,38] Iatrogenic CGE generally involves smaller bubble and dissolved nitrogen loads compared to diving injuries. Therefore, the increased health and safety risks for in-chamber attendants[39] and limited evidence of increased efficacy[40] means that these deeper tables cannot be justified and they have been replaced largely by either the standard DCI treatment table (RN 62) or a shorter 284 kPa table (RN 61).

Cardiothoracic surgery has a relatively high incidence of CGE compared to other surgical specialties. It is for this reason that most centres have developed air embolism protocols which include rapid detection, placing the patient in steep head-down position,[41] commencing a lignocaine infusion,[42,43] contacting a hyperbaric service and considering retrograde cerebral perfusion. This and other studies suggest that protocols may not be adopted even when the hospital has a hyperbaric unit onsite. Potential explanations include either lack of detection at the time of gas entrainment, visualisation of gas in the bypass circuit being deemed small and clinically insignificant and uncertainty around the diagnosis prompting subsequent imaging and further time delay to starting HBOT.

Sometimes the first indication of CGE is hemiplegia or blindness on awakening from sedation or anaesthesia many hours after the precipitating event.[2] Efforts should be made to increase awareness of this significant complication to aid early detection. Familiarity with local gas embolism protocols, including the institution of ancillary treatments, should be gained and mandated in the event of CGE detection regardless of gas volume or perceived clinical significance.

Imaging with MRI or CT may support a diagnosis of CAGE but is rarely conclusive.[44] Therefore it is generally unwise to delay HBOT for the sake of image procedures unless the results will dramatically alter the immediate care.

This study has a number of limitations. Firstly, as with many retrospective studies, it is not possible to adequately generate matched comparator groups of patients with similar disease severity. If the diagnosis is obvious, the decision to refer to a hyperbaric unit largely depends on the proceduralist involved. Considerations include familiarity and previous experiences with hyperbaric units, the size and perceived clinical consequences of the gas and the logistics of inter-hospital transfer if the event had occurred outside The Alfred Hospital.

Transferring a potentially unstable patient over large distances would be a deterrent for many doctors and this introduces both selection and treatment bias. As nearly two-thirds were Alfred in-patients, it is possible that only those non-Alfred patients stable enough to be transported have been studied. Therefore, the overall mortality from gas embolism in our hospital community could be higher than reported. Since it is believed that the size of the gas

embolism has no correlation with neurological insult, all patients with known or suspected CGE should be referred for consideration of HBOT and transferred if safe to do so.[13]

Secondly, patient inclusion in this study was dependent on ICD coding at discharge or death. CGE is a clinical diagnosis and so depends on the treating surgeon or interventional radiologist to diagnose it and document the incident. It also relies on the correct interpretation of medical records and operation reports by clerical staff so that the relevant ICD codes can be applied to the patient.

Thirdly, the GOS-E provides an overall assessment of neurological outcome but does not provide detailed information pertaining to specific disabilities or level of independence. Categories are crude and subject to interpretation. The scale does not reflect subtle improvements in functional status of the individual so that a considerable improvement in ability still may not change outcome category.[20] The GOS-E was primarily intended to provide an overall summary of outcome and facilitate comparison rather than describe specific areas of dysfunction.[20] Furthermore, outcome categories are expressed as a dichotomy: poor/unfavourable outcome versus independence/favourable outcome. This results in a loss of information and decreased sensitivity.[21] In addition, there is no current way of assessing a patient's neurological injury at the time of diagnosis. One can only rely on clinical impressions such as haemodynamic instability to infer the degree of neurological insult.

Conclusion

Hyperbaric oxygen therapy is the mainstay of treatment for CGE. This study suggests that early recognition and treatment does improve neurological outcome. In some instances, benefits of treating with HBOT may extend up to 24 hours or more after the precipitating event. If CGE is recognised or even suspected, CGE protocols should be activated and adhered to, including early referral to a hyperbaric unit. This should occur irrespective of gas load or perceived clinical significance.

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