BRIEF REPORT

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Seizures in Iatrogenic Cerebral Arterial Gas Embolism

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OBJECTIVES: Iatrogenic cerebral arterial gas embolism occurs when gas enters the cerebral arterial circulation during a medical procedure and is considered a severe complication. Seizures have been described in these patients, but information on clinical characteristics, treatment, and outcome is lacking in current literature. The aim of the study was to explore seizures in patients with iatrogenic cerebral arterial gas embolism and to evaluate management strategies.

DESIGN: Retrospective single-center observational study.

SETTING: The only university hospital in the Netherlands with a hyperbaric oxygen therapy facility.

PATIENTS: All patients presenting at or referred to our center with iatrogenic cerebral arterial gas embolism between May 2016 and December 2020.

INTERVENTIONS: Not applicable.

MEASUREMENTS AND MAIN RESULTS: Fifteen patients with iatrogenic cerebral arterial gas embolism were identified, of whom 11 (73%) developed seizures. Five patients developed their first seizure prior to hyperbaric oxygen therapy, three during hyperbaric oxygen therapy, and three after hyperbaric oxygen therapy. Of the 11 patients with seizures, all but one were treated with anti-epileptic drugs. With a median follow-up time of 5 months (range, 1–54 mo), five patients showed complete neurologic recovery, five had minor neurologic deficit, two had moderate to severe neurologic deficit, and three had died. Four patients still used anti-epileptic drugs at follow-up. No patients had recurrent seizures after hospital discharge.

CONCLUSIONS: `Seizures are a common symptom in iatrogenic cerebral arterial gas embolism. They are often treated with anti-epileptic drugs and do not seem to lead to chronic epilepsy.

KEY WORDS: air embolism; brain ischemia; epilepsy; hyperbaric oxygenation; seizures; stroke

Cerebral arterial gas embolism (CAGE) occurs when gas, usually air, enters the cerebral arterial circulation. This may happen through direct intra-arterial injection of gas or indirectly by venous gas traveling through a pulmonary or cardiac right-left shunt (1). The occurrence of gas embolism is often attributable to an invasive medical procedure. Many different medical procedures have been related to iatrogenic CAGE, including central venous line placement, thoracic procedures, and cardiac surgery (2, 3). The occurrence of this rare but serious adverse event has not been well established, but one study reports an incidence of iatrogenic gas embolism requiring hyperbaric oxygen therapy (HBOT) of 2.65 per 100,000 hospital admissions (2).

A previous systematic review of case reports found that almost 20% of patients with cerebral gas embolism developed epileptic seizures (3). Information on patient characteristics, type of seizures, timing of seizures, treatment, and

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outcome is lacking in current literature. The objective of this observational study is to explore seizures in iatrogenic CAGE patients in further detail and to evaluate management strategies.

MATERIALS AND METHODS

This single-center observational cohort study was performed in Amsterdam University Medical Centers, location Academic Medical Center (AMC), the only university hospital in The Netherlands with an HBOT facility. We retrospectively analyzed all patients presenting at or referred to our center with iatrogenic CAGE between May 2016 and December 2020. The local ethics committee reviewed the study and waived the requirement for formal approval (Amsterdam University Medical Centers, location AMC, institutional review board number W21_275 number 21.302).

After obtaining consent from each patient, data were extracted from the electronic patient file and missing data were collected from referring centers. The original radiology images and reports were used to assess imaging. Follow-up data were obtained through telephone interviews conducted by the first and last author. Functional outcome at the time of the interview was measured using the modified Rankin Scale (mRS), a commonly used tool to assess disability after stroke (0: no symptoms, 1: no significant disability, 2: slight disability but functional independence, 3: moderate disability requiring some assistance, 4: moderately severe disability requiring assistance for walking and bodily needs, 5: severe disability requiring constant care, 6: dead). Due to the explorative nature of the study with a small number of patients, only descriptive statistics were used.

The treatment protocol for CAGE in our institution corresponds to international standards (4). After ruling out any continuing introduction of air into the vasculature, vital parameters are stabilized, including intubation and ventilation if required. If seizures are present, they are terminated with IV midazolam, followed by loading and maintenance with an anti-epileptic drug (AED). Normobaric hyperoxia is applied in all patients (either through the endotracheal tube or with high-flow oxygen through a nonrebreathing mask). CT scan of the cerebrum is performed only in cases where the diagnosis of CAGE cannot be made clinically or if other causes of acute neurologic deterioration need to be ruled out. HBOT is instituted as soon as possible, unless contraindicated. The most important contraindication for HBOT is a pneumothorax that cannot be adequately drained. If patients are referred to us from other facilities, we recommend to follow our treatment protocol as closely as possible.

HBOT is performed according to the internationally accepted standard (4) using U.S. Navy treatment table 6 (**Fig. 1**) as the first treatment table. This treatment table consists of initial compression to 2.8 atmosphere (284 kPa) for 75 minutes, followed by gradual decompression to 1.9 atmosphere (193 kPa), which is maintained for 150 minutes, followed by gradual decompression to normal pressure. Additional treatment sessions with HBOT are given if a patient demonstrates clinical improvement after the first treatment. If additional HBOT is performed, this is done using an HBOT table (Fig. 1) that consists of compression to 2.4 atmospheres (243 kPa) for 90 minutes. Use of this table for follow-up treatment in CAGE is a commonly accepted procedure (4).

RESULTS

During the study period, 15 patients with iatrogenic CAGE were identified (**Table 1**). Detailed information can be found in the **Supplemental Table** (http://links.lww.com/CCX/A757). Causative events were mainly thoracic procedures. Presenting symptoms mostly consisted of focal neurologic deficit and impaired consciousness. All patients were treated with HBOT, except one patient who had minor neurologic deficit and increased risk of complications because of severe preexisting lung disease.

During hospitalization, 11 patients (73%) developed seizures, five of whom had more than one seizure. Five patients developed their first seizure prior to HBOT, three during HBOT, and three after HBOT. Of the three patients with their first seizure during HBOT, one patient (patient 6 in the Supplemental Table, http://links.lww.com/CCX/A757) had their first seizure while on oxygen at a pressure of 1.9 atmosphere (193 kPa). Discontinuation of hyperoxia did not end the seizure, treatment with midazolam did. HBOT was completed with no further seizures, but the patient did have recurrent seizures after HBOT. The second patient (patient 7 in the Supplemental Table, http://links.lww.com/CCX/A757) had their first seizure on oxygen, near the end of the second HBOT session, when pressure was almost back to 1 atmosphere (101 kPa). One minute after hyperoxia was ceased, the seizure ended. This patient also had recurrent seizures after HBOT.

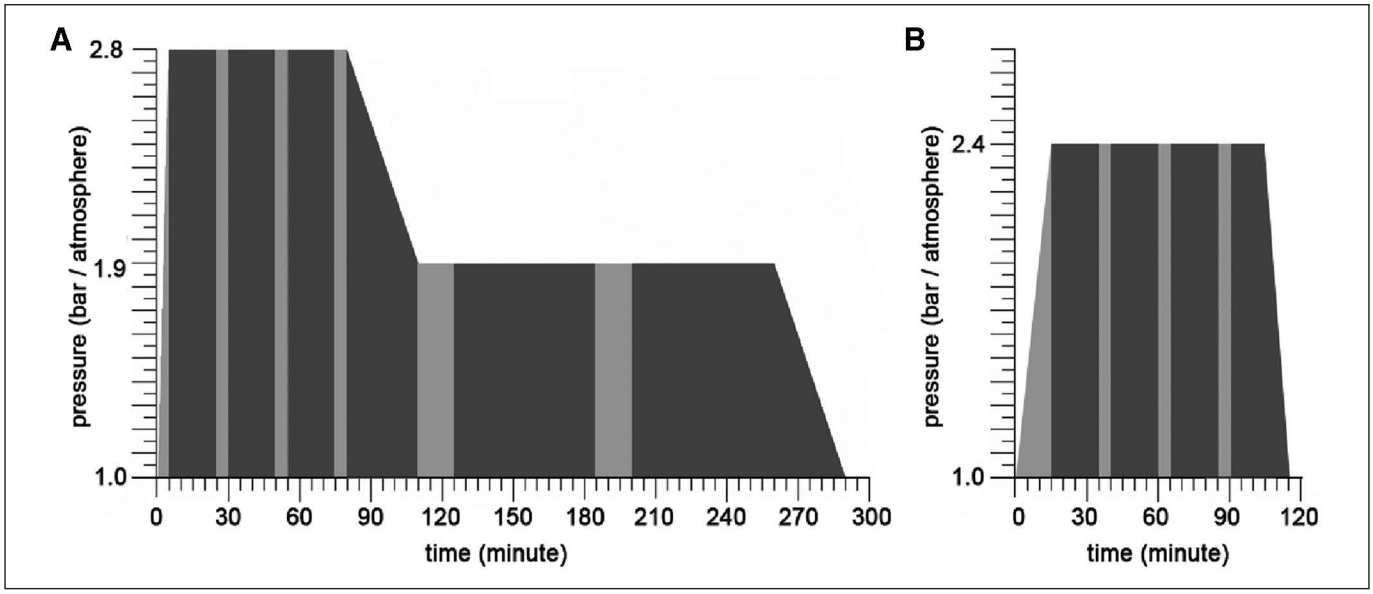

Figure 1. Hyperbaric oxygen treatment tables. **A**, U.S. Navy treatment table 6 as was used in all initial treatments. Treatment consists of initial compression to 2.8 atmosphere (284 kPa) for 75 min, followed by gradual decompression to 1.9 atmosphere (193 kPa), which is maintained for 150 min, followed by gradual decompression to normal pressure. Total treatment lasts just under 5 hr. Oxygen breathing (*dark gray*) is interspersed with short periods of air breathing (*light gray*) to lower the risk of oxygen toxicity. **B**, Regular hyperbaric oxygen treatment table as was used if patients received a second treatment session. Treatment consists of compression to 2.4 atmosphere (243 kPa) for 90 min and includes three air (instead of oxygen) breathing periods to reduce the risk of oxygen toxicity. Total treatment lasts 115 min.

The third patient (patient 10 in the Supplemental Table, http://links.lww.com/CCX/A757) had their first seizure while on oxygen at a pressure of 2.8 atmosphere (284 kPa). The seizure terminated shortly after hyperoxia was withdrawn. Levetiracetam was administered. Later during the course of the HBOT session, on oxygen at a pressure of 1.9 atmosphere (193 kPa), a second seizure was observed, which subsided after titration of midazolam. This patient did not have recurrent seizures after HBOT.

In three patients, electrical encephalography was performed because of prolonged impairment of consciousness. They were all standard recordings of approximately 30 minutes. None of the recordings showed epileptiform abnormalities. Brain imaging was performed in all 15 patients, showing intracranial air in 10 patients (67%). In the other patients, CAGE was diagnosed based on acute neurologic symptoms preceded by a medical intervention where vascular introduction of air was observed or suspected. Two of the patients without intracranial air did not undergo the first brain imaging until after HBOT. In one patient, an MRI scan of the brain was acquired in the acute phase, showing focal ischemia. All other patients underwent CT imaging in the acute phase, none of which showed ischemia. In nine patients, follow-up imaging was performed (MRI in two patients, CT in seven) showing focal ischemia in six patients and focal areas of edema in three. The foci of ischemia and edema on imaging corresponded with symptoms in patients with focal neurologic deficit. In four patients with seizures, no imaging abnormalities were found, although three of them did not undergo any follow-up imaging.

Of the 11 patients with seizures, all but one were treated with AED (Table 1). Details regarding doses can be found in the Supplemental Table (http://links.lww.com/CCX/A757). If patients were treated with benzodiazepines and/or AED, this was done during or directly after the seizure, increasing dosages or adding another drug in case of recurrence. With a median follow-up time of 5 months (range, 1–54 mo), five patients showed complete neurologic recovery (mRS 0), five had minor neurologic deficit (mRS 1–2), two had moderate to severe neurologic deficit (mRS 3–5), and three had died. Cause of death was sequelae of the gas embolism in two patients, both with persistent coma after extensive ischemic brain damage. One patient died of coronavirus disease 2019. Four patients still used AED at follow-up. No patients had recurrent seizures after hospital discharge.

TABLE 1.
Patient Characteristics, Clinical Symptoms, Imaging Findings, Treatment, and Outcome

Characteristics	Total Cohort (*n* = 15)
Age, median (range)	68 (25–85)
Sex, female, *n* (%)	8 (53)
Presenting signs	
Impaired consciousness	7
Focal neurologic deficit	10
Seizure	2
Procedure	
Lung biopsy	5
Chest tube placement and/or lavage	3
Removal jugular central venous catheter	2
Direct arterial introduction of air	2
Direct venous introduction of air	1
Bronchoscopy	1
Gastroscopy	1
Seizure, *n* (%)	11 (73)
Acute imaging, *n* (%)	14 (93)
CT	13
MRI	1
Findings acute imaging	
Intracranial air	10
Focal edema	3
Ischemia	1
Treatment with HBOT, *n* (%)	14 (93)
Sedation and invasive ventilation, *n* (%)	6 (40)
Before HBOT	5
After HBOT	1
Findings follow-up imaging, *n* (%)	9 (60)
Focal edema	3
Ischemia	6
None	2
Medication	
Benzodiazepine, *n* (%)	6 (55)
AED, *n* (%)	10 (91)
Levetiracetam	9
Valproic acid	2
Phenytoin	1
Recurrent seizures at follow-up	0
AED at follow-up, *n* (%)	4 (27)

AED = anti-epileptic drug, HBOT = hyperbaric oxygen therapy. Modified Rankin Scale: 0 no symptoms, 1 no significant disability, 2 slight disability but functional independence, 3 moderate disability requiring some assistance, 4 moderately severe disability requiring assistance for walking and bodily needs, 5 severe disability requiring constant care, and 6 dead.

DISCUSSION

We found that approximately three-quarters of patients with iatrogenic CAGE had one or more epileptic seizures. This is notably higher than has previously been reported. In a prospective cohort of 125 patients with iatrogenic gas embolism, a seizure incidence of 30% was found (2). This, however, did not specifically concern patients with cerebral localization of gas embolism. A review of case reports of patients with iatrogenic cerebral gas embolism described 187 patients with neurologic symptoms, 20% of whom had one or more seizures (3). Early seizures occur in around 5% of patients with acute ischemic stroke and in about 8% of patients with hemorrhagic stroke (5). The occurrence of seizures in CAGE seems to be significantly higher than in these more common cerebrovascular diseases.

The underlying mechanism of early seizures after stroke has not been fully established and is thought to be different for early seizures than for late seizures. It is hypothesized that early seizures are caused by temporary metabolic changes in the neuronal network due to hypoxic damage, leading to alterations in electrolyte concentrations and release of excitatory amino acids such as glutamate, lowering the threshold for neuronal depolarization, and thus causing a state of hyperexcitability (6). In CAGE, arterial flow is blocked by the air bubbles, leading to distal ischemia and the above-described cascade of metabolic imbalance. Furthermore, the air bubbles may cause local damage due to an inflammatory response triggered by the bubble surface, as well as mechanical endothelial irritation causing disruption of the blood-brain barrier (1). Although most patients with seizures in our cohort had focal edema or ischemia on brain imaging, seizures were also seen in patients without any imaging abnormalities, suggesting that the abovementioned mechanisms may occur without underlying structural damage.

All but one patient in our cohort underwent HBOT. Seizures as a result of oxygen toxicity are a known adverse event of HBOT (7). The mechanism is thought to be an excitatory effect of reactive oxygen species (7). Although susceptibility to cerebral oxygen toxicity is highly variable, it generally does not occur below partial oxygen tensions of 2.4 bar (i.e., at an atmospheric pressure of 2.4 bar [243 kPa] when 100% oxygen is breathed) during hyperoxia in a hyperbaric chamber (7). However, it is conceivable that in CAGE, the injured

brain is more susceptible to oxygen toxicity. Three patients in our cohort had their first seizure during HBOT. Two of these patients showed no signs of oxygen toxicity during the period of the highest oxygen tension, but instead later during HBOT when oxygen tension was already lowered. Furthermore, these patients had recurrent seizures after the HBOT was finished. In these two patients, therefore, oxygen toxicity does not seem to be the cause of the seizure. The third patient experienced the first seizure during maximal oxygenation, responded favorably to removal of hyperoxia, and did not have recurrent seizures after HBOT. In this patient, oxygen toxicity may very well have contributed to the seizure.

Almost all patients with epilepsy in our cohort were treated with AED, in most cases preceded by a benzodiazepine. Used AEDs were levetiracetam, valproic acid, and phenytoin, similar to widely used drugs in post-stroke epilepsy. In most patients, AEDs were discontinued after hospital discharge, yet no patients had recurrent seizures after discharge. CAGE-related seizures thus do not seem to lead to chronic epilepsy, as is seen in one-third of patient with early post-stroke seizures (8). Although prophylactic AED in stroke patients have been used in the past, they are currently not recommended in guidelines, as there is no evidence for their benefit and, in some studies, they have been associated with a poorer outcome (6, 9, 10). Considering the markedly higher incidence of early seizures in CAGE, however, temporary prophylactic treatment is to be considered, especially in order to prevent patients from having a seizure during HBOT, leading to an inconvenient and potentially dangerous situation. Current guidelines on gas embolism make no mention of adjunctive therapy with AED (4).

Some patients with CAGE (40% in our cohort) will require intubation and mechanical ventilation, and will therefore be sedated, which is usually effective prophylaxis for epilepsy. Routine sedation and intubation of CAGE patients in order to prevent seizures during HBOT, however, are undesirable since mechanical ventilation inside a hyperbaric chamber—albeit safely possible—is cumbersome, and sedation removes the possibility of continuous monitoring of neurologic function. However, based on the high incidence of epilepsy after CAGE, one might consider a lower threshold for sedation and intubation than in other types of ischemic stroke. This may specifically be the case in patients with hypoventilation due to impaired consciousness since hypercapnic vasodilation predisposes for cerebral oxygen toxicity (7).

CAGE is a rare but serious complication of invasive medical procedures. Although all invasive procedures carry a risk of air entering the vasculature, manipulation of a central venous catheter, lung biopsy, cardiopulmonary bypass, and angiography have been most often described in case reports as the causative procedure (3). CAGE is a clinical diagnosis, imaging is only recommended if needed to rule out alternative diagnoses (4). In practice, CAGE is often not immediately suspected on clinical grounds, and the diagnosis is usually made when cerebral imaging demonstrates intravascular air bubbles. Treatment consists of cessation of entrance of air into the vasculature, stabilization of vital parameters using 100% oxygen, and expeditious start of HBOT. Hyperoxia serves primarily to denitrogenate the body and thereby provide a gradient for efflux of nitrogen out of the gas bubbles. The greatly increased partial oxygen tensions achieved during HBOT enhances denitrogenation, and additionally, the increased atmospheric pressure itself compresses the bubbles, thereby speeding up their clearance from the arteries. HBOT is highly effective when it is started immediately after occurrence of symptoms, for instance, when CAGE is caused by pulmonary barotrauma in submarine escape trainees (where a recompression chamber is often available at the training location) (11). In iatrogenic CAGE, HBOT is rarely immediately available and is often delayed for several hours, which may have a negative impact on outcome. In a large prospective cohort, delay until start of HBOT of more than 7 hours was associated with worse neurologic outcome (2). A clinical trial including a treatment arm without HBOT has never been performed, but given the clear effect of immediate HBOT in submarine escapees, it is unlikely that it ever will be.

To our knowledge, this is the first study focusing on seizures in clinical patients with CAGE. Our study is limited by the relatively small number of patients making the data unsuitable for associations and restricting the study to an explorative character. Our patients were collected retrospectively, and due to suboptimal registration, some information was unobtainable. Nonetheless, this cohort gives a first insight into a common complication in patients with an uncommon illness.

CONCLUSIONS

Seizures are a common symptom in iatrogenic CAGE. They are often treated with AED and do not seem to lead to chronic epilepsy.

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