Advances in diagnosis and treatment of cerebral arterial gas embolism

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Citation for published version (APA):
Acute neurological symptoms during hypobaric exposure: consider cerebral air embolism

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Aviat Space Environ Med 2012; 83:1084-91
Abstract

Cerebral arterial gas embolism (CAGE) is well known as a complication of invasive medical procedures and as a risk in diving and submarine escape. In the underwater environment, CAGE is caused by trapped air, which expands and leads to lung vessel rupture when ambient pressure decreases during ascent. Pressure decrease also occurs during hypobaric activities such as flying and, therefore, CAGE may theoretically be a risk in hypobaric exposure. We reviewed the available literature on this subject. Identified were 12 cases of CAGE due to hypobaric exposure. Based on these cases, we discuss pathophysiology, diagnosis, and treatment of CAGE due to hypobaric exposure. The low and slow pressure decrease during most hypobaric activities (as opposed to diving) account for the low incidence of CAGE during these exposures and suggest that severe air trapping must be present to cause barotrauma. This is also suggested by the large prevalence of air filled cysts in the case reports reviewed. We recommend considering CAGE in all patients presenting with acute central neurological injury during or shortly after pressure decrease such as flying. A CT scan of head and chest should be performed in these patients. Treatment with hyperbaric oxygen therapy should be initiated as soon as possible in cases of proven or probable CAGE.
**Introduction**

The introduction of air into the cerebral arteries (cerebral arterial gas embolism, CAGE) has been regularly described as a complication of invasive medical procedures. CAGE is a serious disorder not only due to the ischemic injury to the brain caused by lodging of air bubbles, but also because of the damage the air bubbles inflict on the blood-brain barrier. CAGE can cause slight transient neurological symptoms, but many patients experience more severe neurological dysfunction and often suffer permanent deficits (1).

Apart from iatrogenic introduction of air, CAGE is a well-known complication in diving and submarine escape. In these cases, air introduction is thought to result from pulmonary barotrauma due to increasing gas volume as surrounding pressure decreases during ascent. In the presence of pulmonary disease with air trapping, but also in healthy lungs when the subject fails to exhale, this increased pressure leads to lung rupture, with ensuing entry of air into the pulmonary venous system and thence via the heart to the brain.

Every day, millions of people are subjected to pressure change due to activities other than diving, for instance when flying or mountaineering. Although

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**Figure 1. Search strategy.**

- **MEDLINE**: n=1584
  - **MEDLINE**: n=8
- **Embase**: n=2568
  - **Embase**: n=11
- **CINAHL**: n=215
  - **CINAHL**: n=2
- **Rubicon**: n=285
  - **Rubicon**: n=0

- **check title/abstract/fulltext:**
- **remove duplicates:**
- **check references:**
- **exclude unproven cases:**
  - n=11
  - n=13
  - n=12
the amount and speed of pressure change involved in these activities is usually much less than in the underwater environment, the large quantity of persons involved suggests that there should be some incidence of CAGE due to these activities. In this review, we summarize the literature available on CAGE due to hypobaric activities. We investigate the published cases and make recommendations on diagnosis and therapy. This review does not focus on decompression sickness (DCS) in the hypobaric environment. Reviews are available on this topic (2).

<table>
<thead>
<tr>
<th>Case</th>
<th>Ref</th>
<th>Sex / Age (y)</th>
<th>Medical history</th>
<th>Activity</th>
<th>Onset of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(3)</td>
<td>F 19</td>
<td>healthy</td>
<td>flying</td>
<td>10-15 min after take-off</td>
</tr>
<tr>
<td>2</td>
<td>(4)</td>
<td>M 45</td>
<td>healthy except smoker</td>
<td>chamber</td>
<td>1 min after descent to 25000 ft after ascent to 30000 ft at 3000 ft/min</td>
</tr>
<tr>
<td>3</td>
<td>(5)</td>
<td>F 40</td>
<td>healthy</td>
<td>flying</td>
<td>10 min after take-off</td>
</tr>
<tr>
<td>4</td>
<td>(6)</td>
<td>M 43</td>
<td>previous aeromedical examination normal</td>
<td>chamber</td>
<td>at 18000 ft during ascent to 25000 ft</td>
</tr>
<tr>
<td>5</td>
<td>(7)</td>
<td>M 43</td>
<td>asthma, smoker</td>
<td>flying</td>
<td>20 min after take-off</td>
</tr>
<tr>
<td>6</td>
<td>(8)</td>
<td>M 71</td>
<td>multiple&lt;sup&gt;a&lt;/sup&gt;</td>
<td>flying</td>
<td>shortly after take-off</td>
</tr>
<tr>
<td>7</td>
<td>(9)</td>
<td>F 62</td>
<td>not mentioned</td>
<td>flying</td>
<td>20 min after take-off</td>
</tr>
<tr>
<td>8</td>
<td>(10)</td>
<td>M 17</td>
<td>not mentioned except non-smoker</td>
<td>flying</td>
<td>15 min after take-off</td>
</tr>
<tr>
<td>9</td>
<td>(11)</td>
<td>M 68</td>
<td>1x LOC during flight, pulmonary cyst on CT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>flying</td>
<td>30 min after take-off</td>
</tr>
<tr>
<td>10</td>
<td>(12)</td>
<td>M 60-69</td>
<td>not mentioned</td>
<td>mountaineering</td>
<td>during ascent from 3392 to 11332 ft at 84 ft/min</td>
</tr>
<tr>
<td>11</td>
<td>(13)</td>
<td>F 62</td>
<td>healthy</td>
<td>flying</td>
<td>30 min after take-off</td>
</tr>
<tr>
<td>12</td>
<td>(14)</td>
<td>F 52</td>
<td>2x seizure during flight</td>
<td>flying</td>
<td>during flight</td>
</tr>
</tbody>
</table>

Table 1. Age, gender, history, hypobaric activity and onset of symptoms in the 12 relevant cases. <sup>a</sup> anticoagulant/dialysis, antiphospholipid syndrome, deep vein thrombosis, Sneddon syndrome, coronary artery bypass graft, pacemaker for atrial fibrillation; <sup>b</sup> the patient had experienced loss of consciousness (LOC) during a previous flight, which most likely resulted from cardiogenic emboli from a mural thrombus.
Methods

We performed a literature search to identify all articles regarding CAGE due to hypobaric exposure (figure 1). Our MEDLINE search strategy was (“embolism, air”[mesh] AND (“brain”[mesh] OR “arteries”[mesh])) OR (“embolism”[tiab] AND (“brain”[tiab] OR “cerebrum”[tiab] OR “cerebral”[tiab] OR “arterial”[tiab]) AND (“air”[tiab] OR “gas”[tiab])) and adapted versions of this strategy were used for the Embase, CINAHL and Rubicon. The search was performed in July 2011. Search results were limited to articles in English with no constraints made on publication date. All search results were checked manually and irrelevant articles were excluded. Articles that were only available as meeting abstracts were excluded. References of included articles were checked to obtain additional articles. In total, we included 13 papers, which were all case reports, describing a total of 13 patients. We critically evaluated these cases and classified them as proven, probable, possible or unproven CAGE according to our criteria, which will be discussed in detail below:

1. Clinical suspicion: objective neurological signs occurring during or shortly after pressure decrease.
2. Brain findings: cerebral ischemia on imaging/autopsy.
3. Thoracic findings: thoracic abnormalities consistent with air trapping or pulmonary barotrauma on imaging/autopsy.
4. Signs of other air emboli than CAGE, e.g. livedo reticularis, air in the retinal arteries, myocardial ischemia.

Where:

Proven CAGE = air in the cerebral arteries;
Probable CAGE = [1] and at least two of [2], [3], or [4];
Possible CAGE = [1] and one of [2], [3], or [4].

Table 1-4 list the characteristics of all 12 cases that were classified as proven, probable or possible CAGE. The reason for rejection in the case
that was classified as unproven was that no brain or chest imaging was performed and, therefore, no proof of CAGE was present except the clinical presentation of the patient (15). In the following paragraphs we will discuss the considerations regarding pathophysiology, diagnosis, and treatment of CAGE due to hypobaric exposure, based on the findings in the 12 patients in which we deemed CAGE was proven, probable or possible.

Case reports

Of the 12 cases, nine occurred during flight, two occurred during hypobaric chamber training, and one patient experienced symptoms during mountaineering (table 1). All in-flight cases occurred on commercial airplanes and none of the articles report any technical malfunction that may

<table>
<thead>
<tr>
<th>Case</th>
<th>Chest symptoms</th>
<th>Neurological signs (objective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>GCS 4-5, myopic unreactive pupils, extensor posturing L</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
<td>dysarthria, L hemiparesis arm/leg/face, L hemisensory deficit</td>
</tr>
<tr>
<td>3</td>
<td>chest pain, dyspnea</td>
<td>comatose, seizures, absent brain stem and deep tendon reflexes, bilateral Babinski</td>
</tr>
<tr>
<td>4</td>
<td>discomfort, dyspnea</td>
<td>mild disorientation and R homonymous hemianopia</td>
</tr>
<tr>
<td>5</td>
<td>dyspnea</td>
<td>unconscious, then GCS 7, L hemiparesis (upper motor neuron signs), decorticate posturing R</td>
</tr>
<tr>
<td>6</td>
<td>discomfort R</td>
<td>GCS 3</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>GCS 3, clonus L lower leg</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>temporary unconscious, on admission bulbar palsy and L hemiparesis</td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>unconscious, bilateral extensor posturing</td>
</tr>
<tr>
<td>10</td>
<td>none</td>
<td>GCS 3, pinpoint pupils</td>
</tr>
<tr>
<td>11</td>
<td>none</td>
<td>CGS 5-6, absent gag and deep tendon reflexes, extension L, Babinski L</td>
</tr>
<tr>
<td>12</td>
<td>dyspnea</td>
<td>seizure, GCS 5</td>
</tr>
</tbody>
</table>

Table 2. Chest symptoms and neurological signs. GCS = Glasgow Coma Scale.
have resulted in increased or rapid decompression. All of these patients first reported symptoms shortly after takeoff (10-30 min) except in one article which only states that symptoms started ‘during flight’. One of the hypobaric chamber related cases occurred after ascent to 30000 ft (9144 m) at 3000 ft/min (914.4 m/min) and subsequent descent to 25000 ft (7620 m), symptoms started after 1 min at 25000 ft. The other hypobaric chamber case occurred during ascent at 1400 ft/min (426.7 m/min) at an altitude of 18000 ft (5486 m). In the mountaineering case the patient was on his way from 3392 ft (1034 m) to 11332 ft (3454 m) in a cable cart at 84 ft/min (25.6 m/min), the altitude at which symptoms started is not mentioned. The pressure difference to which the patients were subjected due to their ascent can, in most cases, only be estimated. In the in-flight cases this estimation is based on the fact that cabin altitude in many modern commercial airplanes is maintained at 8000 ft (2438 m) (16) and the assumption that this cabin altitude is reached after about 20 min of climbing. Thus, the estimated pressure decrease before start of symptoms ranged from 13 to 63 kPa.

Seven patients did not report any chest symptoms, while the other five patients reported chest pain or discomfort and/or dyspnea (table 2). Neurological symptoms were variable, so we report only the objective neurological signs. Of the 12 patients, 11 had at least temporarily decreased consciousness, six of whom were comatose (Glasgow Coma Scale < 8). Two patients had generalized seizures. In four patients cranial nerve abnormalities are reported. In nine patients some abnormality of the neurological examination of the extremities was present. Of note, in six of these patients the defects were strictly left sided, mostly consisting of hemiparesis and hemisensory deficit, and purely right sided abnormalities are not reported.

In all patients some form of cerebral imaging was performed, consisting of CT scan in 11 cases and MRI scan in five cases (table 3). Imaging showed abnormalities in nine patients, of whom six showed air bubbles with or without cerebral ischemia and the other patients had cerebral ischemia
and/or edema without visible air. Chest imaging was performed using CT in all patients, except in one in whom only chest radiography was performed. All patients had thoracic lesions, namely bronchogenic cyst (six patients), congenital cystic adenomatoid malformation (two cases), unspecified cystic mass (one patient) and bullae and/or blebs (three cases).

<table>
<thead>
<tr>
<th>Case</th>
<th>Brain evidence</th>
<th>Thoracic evidence</th>
<th>Other air emboli</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>yes (CT: bilateral edema)</td>
<td>yes (X/postmortem: bulla)</td>
<td>no</td>
<td>probable</td>
</tr>
<tr>
<td>2</td>
<td>yes (MRI: ischemia R)</td>
<td>yes (CT: blebs)</td>
<td>no</td>
<td>probable</td>
</tr>
<tr>
<td>3</td>
<td>yes (CT/autopsy: bilateral multifocal ischemia)</td>
<td>yes (CT/autopsy: BC, myocardial ischemia, livedo reticularis)</td>
<td>probable</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>no (CT after 24h normal)</td>
<td>yes (CT/resection: BC)</td>
<td>no</td>
<td>possible</td>
</tr>
<tr>
<td>5</td>
<td>no (CT/EEG normal)</td>
<td>yes (CT: bulla)</td>
<td>yes (myocardial ischemia)</td>
<td>probable</td>
</tr>
<tr>
<td>6</td>
<td>yes (CT: bilateral air)</td>
<td>yes (CT: BC)</td>
<td>yes (myocardial ischemia)</td>
<td>proven</td>
</tr>
<tr>
<td>7</td>
<td>yes (CT: air/edema; MRI: multifocal ischemia)</td>
<td>yes (CT: CCAM)</td>
<td>yes (myocardial ischemia)</td>
<td>proven</td>
</tr>
<tr>
<td>8</td>
<td>no (CT/MRI/EEG normal)</td>
<td>yes (CT: CCAM)</td>
<td>yes (myocardial ischemia)</td>
<td>probable</td>
</tr>
<tr>
<td>9</td>
<td>yes (CT: air; MRI: multifocal ischemia R&gt;L)</td>
<td>yes (CT: BC)</td>
<td>no</td>
<td>proven</td>
</tr>
<tr>
<td>10</td>
<td>yes (CT: air R)</td>
<td>yes (CT: BC, pneumomediastinum, pneumopericardium)</td>
<td>yes (myocardial ischemia)</td>
<td>proven</td>
</tr>
<tr>
<td>11</td>
<td>yes (CT: air; MRI: multifocal ischemia R&gt;L)</td>
<td>yes (CT: cystic mass)</td>
<td>no</td>
<td>proven</td>
</tr>
<tr>
<td>12</td>
<td>yes (CT: bilateral air)</td>
<td>yes (CT: CB)</td>
<td>yes (myocardial ischemia)</td>
<td>proven</td>
</tr>
</tbody>
</table>

Table 3. Brain and thoracic findings, other signs of extrapulmonary air and classification. X = chest X-ray; BC = bronchogenic cyst; CCAM = congenital cystic adenomatoid malformation.
One patient had signs of pulmonary barotrauma, namely pneumomediastinum and pneumopericardium. Seven patients had concurrent myocardial infarction which was thought to result from coronary air embolism. One of these patients also had livedo reticularis of the hands and upper thorax as a sign of systemic air embolization.

Five patients were treated with hyperbaric oxygen therapy (HBOT), but complete data regarding the treatment (delay until start, types, and amounts of sessions) are available in only two cases (table 4). The reason for not instituting HBOT was given in four of the seven cases, being that the patient was too ill (two patients), that too much delay had already occurred (one patient) and that the patient had spontaneously recovered (one patient). Six patients died, four patients recovered completely, one patient had severe permanent deficits, and one patient initially recovered but then died of pulmonary embolism.

<table>
<thead>
<tr>
<th>Case</th>
<th>Hyperbaric oxygen therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no (no reason)</td>
<td>death</td>
</tr>
<tr>
<td>2</td>
<td>yes (delay 2.5 h, 3 sessions (1x extended table 6A, 2x 90 min at 2 ATA))</td>
<td>complete recovery</td>
</tr>
<tr>
<td>3</td>
<td>no (too ill)</td>
<td>death</td>
</tr>
<tr>
<td>4</td>
<td>yes (delay unknown, 4 sessions)</td>
<td>complete recovery</td>
</tr>
<tr>
<td>5</td>
<td>yes (delay 48h, 2 sessions (8h HeO2 table starting at 6 ATA))</td>
<td>complete recovery</td>
</tr>
<tr>
<td>6</td>
<td>no (too much delay (48-72h))</td>
<td>death</td>
</tr>
<tr>
<td>7</td>
<td>no (no reason)</td>
<td>severe disability</td>
</tr>
<tr>
<td>8</td>
<td>no (spontaneous improvement at 72h)</td>
<td>complete recovery</td>
</tr>
<tr>
<td>9</td>
<td>yes (delay unknown, 1 session)</td>
<td>death</td>
</tr>
<tr>
<td>10</td>
<td>no (no reason)</td>
<td>death</td>
</tr>
<tr>
<td>11</td>
<td>no (too ill)</td>
<td>moderate recovery, then death (pulmonary embolism)</td>
</tr>
<tr>
<td>12</td>
<td>yes (delay &gt;2 h, 1 session?)</td>
<td>death</td>
</tr>
</tbody>
</table>

Table 4. Treatment and outcome. ATA = atmospheres absolute.
Pathophysiology

A number of reviews have addressed the pathophysiology of CAGE (1, 17, 18). We will give a brief summary of this subject with special interest in the differences between hyperbaric and hypobaric origin of CAGE. Noniatrogenic CAGE is best known in diving medicine. In these patients, the etiology of air introduction is pulmonary barotrauma with subsequent flow of air into the pulmonary venous vasculature and thence to the systemic arterial circulation. In order for air to flow from the lungs into the vessels, some degree of air trapping in conjunction with decrease of ambient pressure must be present. Under these circumstances, the trapped air will expand as dictated by Boyle’s law, which states that pressure and volume are inversely proportional (19). This expanded air may cause volume increase of the space in which the air is contained, causing stretching of the wall of the structure, which may lead to vessel rupture. Apart from CAGE, escaping air may also cause pneumothorax, pneumomediastinum, and subcutaneous emphysema. While some patients with CAGE may concurrently have one or more of these other signs of lung damage, in many patients CAGE is the sole manifestation of pulmonary barotrauma.

It is important to realize that pulmonary barotrauma can occur even when the trapping of air is not complete (i.e., there is some degree of communication between the trapped air and the rest of the bronchial tree) as long as there is relative air trapping, meaning the escape of air from the contained space cannot keep up with the ambient pressure decrease. CAGE can even occur in healthy persons without thoracic abnormalities when ambient pressure decreases while the subject fails to exhale, due to active breath-holding or, for instance, laryngospasm (20).

The above-mentioned etiology of noniatrogenic CAGE explains why this disease is so much better known in diving medicine than in other types of dysbaric activities such as flying. Arterial gas embolism was the cause of 3% of diving fatalities and 33% of diving accidents resulting
in disabling injury in the 2008 Diver’s Alert Network report (21), while our current search on hypobaric CAGE yielded only 12 published cases throughout the literature. There are numerous differences between the underwater and the hypobaric situation that explain the higher incidence in the underwater environment (22). First of all, the amount of pressure difference involved in underwater activities is much higher than during flying. In commercial airliners cabin altitude is required by law to be maintained at a maximum of 8000 ft (2438 m) under normal operating conditions, which corresponds to a pressure of approximately 75 kPa or about 26 kPa difference compared to ground level pressure. During diving, this pressure difference is reached by descending only approximately 10 ft (≈3 m). Nevertheless, the pressure decrease in most hypobaric activities is theoretically large enough to cause barotrauma, given the fact that Malhotra and Wright observed pulmonary damage at transpulmonary pressures of 9.7 kPa (23). This pressure decrease is achieved by ascending to as little as 2700 ft (823 m). In all of the cases described in this review the pressure difference to which the patients were subjected was larger than 9.7 kPa.

The second reason for the low incidence of CAGE due to hypobaric activities is the lower speed of pressure decrease involved when compared to underwater activities. When decompression occurs at a higher rate, even air collections that partly communicate with the bronchial tree may cause pulmonary barotrauma since the pressure decrease occurs so rapidly that the escape of air cannot keep up with its expansion. The slow rate of decompression in, for example, flying may require more profound air trapping in order for barotrauma to occur. Furthermore, in divers and submarine escape trainees, active breath-holding or laryngospasm due to panicking are known to occur, which renders the total lung volume a closed compartment (20). Breath-holding will not be an issue in the hypobaric environment due to the slow pressure decrease. An exception may be rapid decompression, either when trained in a hypobaric chamber or when accidentally sustained during flight. There are cases of suspected CAGE due to rapid decompression during
pressurization of aircraft cabins on the ground (24, 25) and one article describes suspected CAGE after rapid decompression in a hypobaric chamber (15). The articles on decompression on the ground were not included in this review because they did not arise from primarily hypobaric activities and the case of CAGE in a hypobaric chamber (15) was excluded as discussed above.

A third factor that may account for the higher incidence of diving-related CAGE is the fact that immersion causes increased small airway closure and might thus potentiate air trapping. The mechanism responsible is redistribution of venous blood leading to pooling of blood in the lungs due to the smaller effect of gravitation and the usually horizontal position of the diver (26).

In the fourth place, clinical awareness of CAGE is much higher in the diving community than it is in the general population. In any diver who surfaces with neurological symptoms, CAGE will be high in the differential diagnosis. Recent studies show that neurological incidents are responsible for 22-24% of all in-flight medical emergencies requiring telemedical assistance (27, 28). It is possible that some of these patients suffered CAGE but were not diagnosed as such.

The abovementioned arguments suggest that more severe air trapping may be required for a person to sustain hypobaric CAGE than is necessary to develop CAGE in the underwater situation. While Calder reported slight pulmonary abnormalities in many autopsies of divers in whom the suspected cause of death was pulmonary barotrauma (29), the currently reported cases all showed gross thoracic abnormalities consistent with air trapping, for instance bronchogenic cysts. This is not due to our inclusion criteria since taking the requirement for thoracic abnormalities out of our algorithm did not result in more included articles. However, results may be biased due to the fact that clinicians will be more likely to establish a diagnosis of CAGE (and publish the case) if there is an abnormality that can explain the air entrance (sampling bias).
Diagnosis

We consider the patient who presents with acute central nervous system dysfunction. The recognition of CAGE is primarily dependent on clinical suspicion, so it is important for the clinician to elucidate the circumstances in which the complaints occurred. A history of pressure decrease in close temporal relationship with the start of symptoms should trigger the clinician to include CAGE in the differential diagnosis. In these cases, there are mainly three possible diagnoses to consider, as pointed out by Rios-Tejada et al. (4). These are CAGE, neurological DCS, and some other sort of cerebral insult, e.g., transient ischemic attack or cerebrovascular hemorrhage. Distinguishing these diagnoses from each other primarily relies on patient history since in most cases direct evidence pathognomonic for one of the entities will not be present.

A history of risk factors such as hypertension and diabetes may suggest a thrombo-embolic origin, while the presence of pulmonary disease or chest symptoms such as pain or dyspnea may point in the direction of CAGE. During normal commercial flight the risk of DCS is very low, because of the relatively low altitude at which the cabin is maintained. The diagnosis becomes more likely when the patients has had hyperbaric exposure (for instance diving) within 24 h before the flight or when the aircraft has suffered technical malfunctions which lead to higher cabin altitude. There is a known risk of DCS in subjects involved in hypobaric chamber training (30). The time course of the symptoms is also of importance. In CAGE there is usually a close temporal relationship between pressure decrease and start of symptoms, although this may be less evident in hypobaric situations than in diving because of the slower decompression. The onset of symptoms in DCS is usually more delayed (31).

Physical examination is not likely to be able to distinguish between the three diagnostic categories. The neurological examination in CAGE does not differ from that in other central stroke syndromes, as can be seen in the cases reviewed here. There seems to be a preponderance of right
hemispherical ischemia in CAGE, in the literature (32) as well as in the
currently reviewed cases. This is hypothesized to be due to the fact that
the brachiocephalic artery, which supplies the right hemisphere, is the
first branch of the aortic arch and may, therefore, catch the largest amount
of air (22). This criterion, however, cannot be used to reliably distinguish
CAGE from the other causes of neurological injury. Neurological DCS gen-
erally involves the spinal cord, so the presence of spinal cord dysfunction
is suggestive of DCS (31). Air emboli that are propelled from the heart
can disperse to all of the systemic circulation, so signs of other locations
of air embolization (e.g., myocardial infarction, air bubbles in the retinal
arteries, or livedo reticularis) can support the diagnosis of CAGE. Signs
of myocardial infarction (mostly ECG changes and elevated cardiac en-
zymes) were present in 7 of 12 cases presented here.

The presence of gas in the cerebral arteries on brain imaging proves
CAGE or DCS (33). Of the patients reviewed here, 50% had intracerebral
air bubbles on CT. This may again be partly due to sampling bias since a
retrospective series on iatrogenic CAGE showed that most patients had no
air on brain CT (34). The absence of air on brain imaging, therefore, does
not rule out CAGE and DCS. Cerebral imaging is nevertheless important
to rule out conditions such as cerebral hemorrhage. CT is the imaging
modality of choice, since it can be performed quickly and provides the
best way of visualizing cerebrovascular air (14). CT is inferior to MRI in
demonstrating early cerebral ischemia, therefore MRI techniques such as
diffusion weighted imaging may be necessary to demonstrate ischemia
in the first hours (35). In a retrospective study, MRI abnormalities were
present in six of eight patients with CAGE but in only two of eight patients
with DCS, although it must be noted that all MRI scans were made at least
hours after the incident (36). Recently, a case report demonstrated the
possible utility of CT perfusion scanning in demonstrating early cerebral
ischemia in CAGE (37).

Reviews of diving-related DCS and CAGE discourage the use of brain im-
aging because negative results do not rule out the diagnosis and the time
necessary to perform the scan delays start of treatment (18). We believe that in cases of suspected hypobaric CAGE cerebral imaging is warranted since the likelihood of other causes of neurological injury is much higher under these circumstances than in the case of a diver surfacing with neurological symptoms.

The likelihood of CAGE is increased when there is evidence of pulmonary air trapping since this provides an explanation for entrance of air into the vasculature. Air trapping can be present in a multitude of pulmonary diseases such as asthma, chronic bronchitis, and bullous and cystic lung diseases (38). However, as discussed above, the case reports reviewed here suggest that relative air trapping such as present in, for example, asthma may not be enough to cause hypobaric CAGE because of the slow pressure decrease involved in most hypobaric exposures. An air filled cyst was present in 9 of 12 cases reviewed here, suggesting that many patients with hypobaric CAGE will have such a cystic thoracic abnormality. Because the diagnosis of CAGE has important therapeutic implications, we advise to perform a chest CT in all patients suffering neurological injury after hypobaric exposure. The presence of an air-filled cyst is highly indicative of CAGE, especially if there is an air-fluid level suggesting recent hemorrhage. Furthermore, chest CT can demonstrate other manifestations of pulmonary barotrauma, such as pneumothorax, which strongly support the diagnosis of CAGE.

It is important to realize that the suggestions regarding diagnosis made in this article are based on the cases reviewed, which were selected based on a predefined algorithm for diagnosis of CAGE. This could result in a kind of spectrum bias, meaning that had we applied other criteria for establishing the diagnosis of CAGE after hypobaric exposure, we might have come to different conclusions. It is therefore important to critically consider our diagnostic criteria. There is no gold standard for establishing the diagnosis of CAGE, so all algorithms including ours are essentially arbitrary. We regard CAGE to be proven when air is seen in the cerebral arteries on brain imaging. Although this criterion may theoretically include cases of
neurological DCS, this is not problematic in practice since treatment for both disorders is the same. In cases where CAGE is suspected but no intravascular air can be seen on cerebral imaging, we require a combination of: 1) evidence of cerebral ischemia; 2) thoracic air trapping or evidence of pulmonary barotrauma; and 3) signs of other air emboli than CAGE. When at least two of these criteria are present, we regard CAGE to be probable, when only one of these criteria are present the patient is diagnosed with possible CAGE. We are aware that these criteria may lead to over- as well as underdiagnosis of CAGE. Patients who suffer, for instance, thromboembolic stroke while flying and who have concurrent pulmonary disease may be diagnosed with CAGE in this algorithm. Underdiagnosis may occur in cases of small thoracic abnormalities and low volumes of air, when brain and chest CT are both negative. However, this situation is not likely to occur since the small thoracic abnormalities that might be missed by CT are not very likely to cause CAGE in the hypobaric environment.

Treatment

Patients suspected of CAGE should receive high flow oxygen, initiated as soon as possible after the insult. High blood oxygen levels provide a favorable gradient for denitrogenation of the air bubbles and supply oxygen to critically perfused cerebral tissue. General hemodynamic supportive measures may be necessary, especially in cases of massive CAGE or concurrent coronary artery air embolism (1). HBOT is the only specific treatment for CAGE. It reduces cerebral injury by compressing the air bubbles in the cerebral arteries, which promotes passage of the bubbles through the capillaries to the venous circulation. Denitrogenation of the bubbles and oxygenation of brain tissue is significantly enhanced when compared to normobaric oxygen therapy (39). It must be stated that there is no level I evidence for the efficacy of HBOT in CAGE but retrospective studies and case reports have been convincing to such an extent that randomized trials will probably never be undertaken (40). Therefore, many questions regarding the optimal application of HBOT remain. One important unan-
answered question is the maximum delay that can be tolerated before HBOT should be initiated. While good recovery has been documented in patients after more than 24 h delay (41), earlier treatment is associated with better outcome (42). A retrospective study showed that patients treated within 7 h have a better outcome than patients treated after 7 h (43). In light of the significant delay that may occur before patients with suspected CAGE report to a hyperbaric facility, especially in case of in-flight neurological disorders, this small therapeutic window calls for a high clinical suspicion of CAGE and expeditious treatment of eligible patients.

We suggest that patients with proven or probable CAGE according to our criteria should be treated with HBOT according to US Navy Treatment Table 6 as soon as possible after the insult. The small therapeutic window may demand that ancillary investigations be limited to CT scanning of the cerebrum and chest, as discussed above. In case of possible CAGE, the decision whether or not to administer HBOT should be made based on factors such as severity of symptoms, delay from start of symptoms and availability of hyperbaric facilities. As can be seen in table 4 not all patients reviewed here were treated with HBOT. The reasons for not giving treatment were mentioned above. Because of the retrospective nature of this study, it is not possible to determine if HBOT was advantageous in the patients reviewed here.

All patients reviewed in this article had a form of pulmonary or airway disease that may have resulted in air trapping, thus providing a mechanism for air entry during hypobaric exposure. As discussed, this high incidence of pulmonary abnormalities may be biased due to the fact that the diagnosis of CAGE is more likely to be made if a patient suffering neurological injury during hypobaric exposure has a disease that provides an explanation for air entry. Nevertheless, discussion of the safety of hypobaric exposure in the presence of thoracic disease with possible air trapping is warranted. In accordance with guidelines on air travel published by the British Thoracic Society (44) and the Aerospace Medical Association (45), we believe that the large majority of patients with respiratory disease can
endure hypobaric exposure as long as they comply to the requirements set out in these guidelines. A review on travel to altitude in patients with lung disease summarized the literature on hypobaric exposure of subjects with bullous lung disorders and concluded that none of the patients suffered worsening pulmonary function or pneumothorax and that these patients can, therefore, safely travel to high altitude (46).

However, since the case reports reviewed in this article suggest that a substantial part of patients who suffered hypobaric CAGE may be diagnosed with bronchogenic cysts or other cystic abnormalities, the presence of such cysts may be less easily compatible with air travel. We believe that patients with cysts that have given rise to CAGE should be denied hypobaric exposure until their cyst has been removed. However, the large majority of patients with bronchogenic cysts are asymptomatic and most cysts are not filled with air (47). The guidelines of the British Thoracic Society recognize that completely encysted air spaces may expand due to ambient pressure decrease and cause CAGE, while cysts that communicate with the airways pose no such risk (44). The Aerospace Medical Association guidelines state that “the presence of lung cysts or bullae is usually not a problem as long as the airways communicate with the abnormal air collection” (45). While the question whether or not an air filled cyst communicates with the bronchial tree is an important one, unfortunately it is often not possible to assess the amount of communication with certainty (5). Furthermore, even cysts that do communicate with the bronchial tree may be hazardous because a ‘stopcock valve mechanism’ may allow air entry but not air escape (5). Retrospective studies suggest that the majority of people with asymptomatic bronchogenic cysts eventually develop symptoms, mostly due to compression, infection, or hemorrhage within the cyst. The current recommendation is, therefore, to resect all bronchogenic cysts in operable candidates (48, 49). The question is whether or not these asymptomatic patients should be allowed to fly until their cyst has been removed. While there are probably very many people who are unaware of their cyst and who travel by airplane for years without problems, we believe the most prudent approach would be to deny hypobaric exposure to these patients.
Conclusions

According to Van Hulst CAGE should be considered in all patients with central neurological changes when circumstances were such that gas embolism could have occurred (1). This is essentially the case for all acute neurological disorders occurring in flight or during other hypobaric activities. The presence of chest symptoms is an unreliable marker for barotrauma and neurological examination cannot reliably distinguish between CAGE and other central neurological disorders. CT imaging of the brain should be performed in all patients since CT can demonstrate air in the cerebral arteries, which proves the diagnosis of CAGE. If no air is present, cerebral ischemia may be visualized, but results may be false negative in the first hours. Chest CT should be performed to find evidence of pulmonary barotrauma and thoracic abnormalities that may account for air entrance. When CAGE is proven or probable, HBOT must be initiated as soon as possible since it is the only specific treatment for CAGE. We recommend adherence to published guidelines in determining whether or not patients with respiratory disease can be allowed to fly (44, 45). In asymptomatic patients with air filled cysts, the most careful approach is to deny flying until the cyst has been removed.
References

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