Advances in diagnosis and treatment of cerebral arterial gas embolism
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General introduction and outline

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Introduction

The underwater environment presents its human visitors with many unique and interesting challenges. Many of these problems are direct or indirect effects of the increased pressure involved in hyperbaric exposure. The higher partial pressure of oxygen may cause oxygen toxicity, the elevated levels of nitrogen pose a risk of inert gas narcosis as well as decompression sickness, and trace amounts of contaminants in the breathing gas may rise to dangerously high levels when breathed under pressure. Barotrauma may occur due to pressure differences between air spaces and the surrounding environment. The best known example of barotrauma is middle ear squeeze, but damage may occur in any air filled cavity that is not (sufficiently) communicating with the outside world. When such an area of air trapping exists in the lungs, pulmonary barotrauma may occur during decompression from depth. The most intriguing and feared result of pulmonary barotrauma occurs when the escaping air flows into the pulmonary veins and is then transported via the heart to the cerebral arteries. This is termed cerebral arterial gas embolism (CAGE). Apart from pulmonary barotrauma, CAGE may result from direct introduction of air into the systemic circulation. These cases of CAGE are usually the result of some kind of invasive medical procedure, for instance cardiac surgery.

The divers in the service of the Royal Netherlands Navy are involved in a multitude of high-demanding diving operations. Furthermore, the Navy’s submarine personnel is regularly trained on disabled submarine situations, which includes rapid ascent from various depths. These activities carry a risk of pulmonary barotrauma and therefore CAGE. Despite the stringent safety precautions employed in all training and operational underwater activities, occasional cases of CAGE have occurred in active duty Dutch military personnel. It is therefore not surprising that the Navy has great interest in this disorder.

This thesis is the result of a continuous Navy research program into CAGE. In this first chapter, we will provide a general overview of this dis-
ease, outlining etiology, pathophysiology, diagnosis, and treatment. We then proceed with a synopsis of the remaining chapters of this thesis, in which we describe our investigations on diagnosis and treatment of this disorder.

Etiology

There are four possible methods for air bubbles to reach the cerebral circulation (figure 1).

1. Pulmonary barotrauma resulting in air entrance in the pulmonary veins (1). The best known cause of this form of CAGE is diving. When a diver
ascends, the surrounding pressure decreases which causes the air in the lungs to expand (Boyle’s law). This expanding air has to escape through the airways. While this occurs without difficulty in persons without pulmonary abnormalities, problems may arise in cases of air trapping. Air trapping may be present in a variety of pulmonary disorders, such as asthma, emphysema, cysts, bullae, etcetera. Even without pulmonary abnormalities, when a divers fails to exhale during ascent, the whole lung volume becomes a closed compartment. Trapped air during ascent can cause rupture of alveoli, resulting in pneumothorax, pneumomediastinum, subcutaneous emphysema, and/or entrance of air into the pulmonary veins. In the latter case, this air will travel to the left heart and thence to the brain.

2. Direct introduction in the circulation somewhere in the trajectory from the pulmonary veins to the brain (1). These cases are usually iatrogenic in origin. The best known example of this category is cardiac surgery, which may lead to air introduction due to inadequate de-airing of the cardiac chambers (in cases of open chamber surgery) or due to air bubbles originating from the cardiopulmonary bypass system. Other causes of CAGE due to iatrogenic air introduction are for instance carotid and pulmonary surgery.

3. Arterialization of air introduced in systemic veins (2). Air introduced into the systemic venous vasculature will generally flow to the lungs. Since the lung is an excellent filter for air bubbles, this will normally not cause clinical symptoms, although large amounts of air may cause clinically evident pulmonary embolism. Also, these large amounts of air may overload the pulmonary arteries, which results in shunting of air from the pulmonary arteries to the pulmonary veins (3a in figure 1). From there the air may be propelled to the brain. A second method for arterialization of systemically introduced air is through a right-left shunt in the heart, most commonly a patent foramen ovale (3b in figure 1). Arterialization of venous air is termed paradoxical air embolism.
4. Retrograde movement of air in systemic arteries (3, 4). It has been demonstrated that large amounts of air can travel retrogradely through arteries and may thus reach the brain. This can either be due to buoyancy of the air bubbles or due to a volume effect. This is mostly a theoretical possibility, since only very few studies have been published that report this way of embolization of the cerebral arteries.

**Distinction between CAGE and similar disorders**

Other forms of air embolism exist, some bearing close resemblance to CAGE. It is important to understand the differences between these disorders and CAGE.

**Non-cerebral arterial gas embolism**

Air that is propelled into the systemic arterial circulation from the heart may not only lead to CAGE, but may also disperse to the rest of the systemic circulation. In theory, this could lead to ischemia in all parts of the body. The main reason that systemic arterial gas embolism usually doesn’t result in clinical symptoms is the fact that in most organs some degree of collateral circulation exists. One important exception – apart from the brain – is the coronary circulation. In fact, many patients with CAGE also suffer from cardiac ischemia, indicating that some of the air has ended up in the coronary circulation (5).

**Venous gas embolism**

Air may be introduced into systemic veins through various mechanisms (6). An example is opening of non-collapsing cerebral venous sinuses during neurosurgery. When this is combined with a negative pressure (as compared to the heart) in these sinuses, large amounts of air may be sucked in. Air introduced into these and other systemic veins will lodge in the pulmonary arteries and be resorbed there. Large amounts of air may cause symptomatic pulmonary embolism and should be acted upon. Furthermore, as described above, an overloading of the pulmonary arteries may lead to shunting of the
air to the pulmonary veins, possibly leading to CAGE. Secondly, air flowing to the right heart from the systemic veins may pass to the left heart through a patent foramen ovale, leading to paradoxical CAGE.

**Decompression sickness**
While the contents of the gas bubbles in CAGE is determined by the mixture of the gas that was introduced into the circulation (most often air), the bubbles in decompression sickness (also known as caisson disease) contain only nitrogen (7). These bubbles appear when a person is decompressed, for instance when returning to surface after diving. Henry’s law states that the solubility of a gas is proportional to the pressure of the gas. Therefore, during a dive the large partial pressure of inhaled nitrogen causes no problems, since all nitrogen is dissolved in the body. When the person ascends, pressure decreases, causing the nitrogen to come out of solution. When this occurs too quickly, nitrogen bubbles may form. These bubbles can cause local tissue damage but may also lead to vascular occlusion. Although neurological damage due to decompression sickness mostly occurs at the spinal level, some patients may exhibit cerebral neurological abnormalities resembling CAGE.

**Pathophysiology**
In CAGE, the contents of the gas that was introduced into the circulation determines the composition of the bubbles. In most cases, the gas will be air. This is the case in the diver who breathes compressed air, as well as in most iatrogenic cases. However, the bubbles may contain other gases, for example in a diver who uses alternative breathing mixtures or when paradoxical CAGE occurs during laparoscopy (in which case the gas will be carbon dioxide). While the behavior of gas bubbles may differ depending on the contents of the bubbles, the general principles of cerebral damage induced by CAGE are always the same. Throughout this thesis, we will consistently use the term CAGE, although the specific gas used in our studies was air.
CAGE causes cerebral injury in two ways (1). Firstly, the bubbles may lodge in small cerebral arterioles and cause ischemic injury much like solid thrombi do. The difference between gaseous and solid thrombi is the fact that the occlusion caused by gaseous bubbles is always temporary. Small bubbles may lodge for only very short periods, being propelled through the capillaries into the veins in a matter of seconds. On the other hand, large amounts of gas may stay in the vessels for long periods, possibly hours (8). Eventually, all bubbles will shrink due to resorption of the gas, followed by propulsion of the bubble to the venous circulation. The second cause of cerebral injury due to CAGE is damage to the endothelium by the bubbles. It has been demonstrated that even bubbles that are too small to lodge in the arteries for a significant amount of time cause endothelial damage, due to stripping of the glycocalyx and the endothelial cells themselves (9). The resulting leakage is clinically evident as cerebral edema. The endothelial damage furthermore results in an inflammatory and protrombotic response (1, 2).

**Epidemiology**

At first glance, CAGE is a rare disorder. The incidence in diving is difficult to estimate, since generally the denominator (total number of dives) is not known. One study estimated the incidence of CAGE to be approximately 0.025 per 100,000 dives. This number was much higher (11 to 32 per 100,000) in training dives involving rapid ascent (10). A large retrospective series of iatrogenic CAGE estimated the complication to occur in 0.57 per 100,000 hospital admissions (5). However, it is possible that cases involving small amounts of air are regularly missed. This can be illustrated using the example of postoperative cognitive dysfunction. As much as 20-40% of patients undergoing cardiac surgery experience long lasting cognitive decline (11, 12). Although the etiology of this disorder is no doubt multifactorial, CAGE has been implicated as an important contributing factor in several studies (13, 14). Multiple reasons are conceivable why not all patients suffering peroperative CAGE are identified, such as difficulty in
adequately diagnosing cerebral air embolization, delayed recovery due to extended postoperative anesthesia, the difficulty distinguishing CAGE from other causes of peroperative cerebral damage, and insufficient clinical awareness. All in all, the exact incidence of CAGE cannot be determined, but is likely to be higher than reported.

**Clinical presentation**

The symptomatology of CAGE is heterogeneous and primarily depends on the brain regions and amount of air involved. Symptoms range from slight transient neurological dysfunction, such as sensory or motor deficit, to coma and brain herniation. In a recent clinical study 82% of patients diagnosed with clinical CAGE had impaired consciousness, 63% of this group was comatose (15). Symptoms develop suddenly after introduction of the air embolism and may be biphasic, when the initial insult is followed by the development of cerebral edema and increasing intracranial pressure. In surgical patients, symptoms may be masked by general anesthesia (1). Some authors have reported higher incidence of right hemispheric lesions compared to left hemispheric lesions (15). This is supposed to be due to the fact that the brachiocephalic artery, which is the first branch of the aortic arch, catches the largest amount of air coming from the heart. The distinction between CAGE and decompression sickness can usually be made by regarding the timespan between provoking exposure (e.g., diving) and start of symptoms. In CAGE, symptoms generally start during the dive or within 5 min after surfacing, while in decompression sickness it may take up to several hours for symptoms to develop.

Since air bubbles originating from the pulmonary veins or heart can distribute to all of the systemic circulation, signs of systemic embolization can accompany CAGE. One of the most important organs in this regard is the heart, and cardiac ischemia is a frequently encountered concurrent problem in patients with CAGE (5). A second set of problems occurs in patients with pulmonary barotrauma as the cause of CAGE, most often
divers. Apart from air entry into the vessels, the lung damage these patients have sustained may lead to pneumothorax, pneumomediastinum, and subcutaneous emphysema.

**Diagnosis**

The single key element in correctly identifying patients with CAGE is index of suspicion. CAGE should be included in the differential diagnosis in all patients with acute neurological symptoms in whom a possibility of entrance of air into the vasculature has existed (2). This includes divers who surface with neurological symptoms, but also surgical patients, especially in procedures with a high risk of CAGE, such as open chamber cardiac surgery. Concurrent abnormalities such as cardiac ischemia or pulmonary barotrauma (in case of a diver) may point in the direction of CAGE. Imaging of the brain may show air bubbles, but false negatives are common. Cerebral ischemia may be demonstrated on CT or MRI, but all techniques require a certain time before ischemia is adequately visible. In cases where there is a high likelihood of CAGE, such as a diver surfacing with neurological abnormalities, it is therefore advised to initiate treatment immediately, without inducing unnecessary delay due to imaging (7).

**Treatment**

In cases of severe CAGE, especially when concurrent coronary air embolization is present, hemodynamic support may be necessary. Normobaric oxygen therapy should be instituted immediately. Although the use of oxygen in other ischemic conditions is increasingly discussed (16), there exists little doubt on the use of oxygen in CAGE. The reason for this is the fact that in CAGE the primary reason for supplemental oxygen is not oxygenation of the penumbra but creation of a favorable gradient for outflow of nitrogen from the air bubbles (denitrogenation) (2). All other necessary
measures to prevent secondary brain injury (prevention of hypotension, hypo- or hypercapnia, and hyperthermia) should be taken. The only specific treatment for CAGE is hyperbaric oxygen therapy (HBOT), which has important advantages over normobaric hyperoxia. Firstly, the increased atmospheric pressure compresses air bubbles that are still present in the circulation, which promotes passage of these bubbles through the capillaries to the venous circulation. Secondly, 100% oxygen combined with increased atmospheric pressure results in arterial and cerebral oxygen tensions that are significantly higher than in normobaric hyperoxia, leading to higher oxygen availability in the brain (2). In the third place, HBOT has been shown to have anti-inflammatory properties, which mediate the inflammatory response that follows the damage done to the endothelium by the air bubbles (17). Initial HBOT in CAGE is generally performed using US Navy Treatment Table 6, which is comprised of two stages of compres-
sion, the first stage at 2.8 atmospheres absolute and the second stage at 1.9 atmospheres absolute. During the treatment the patient breathes 100% oxygen, with intermittent air breaks to reduce the risk of cerebral oxygen toxicity (18) (figure 2). The treatment can be extended or repeated based on the clinical status of the patient.

**Outcome**

Outcome in patients suffering CAGE varies widely between studies. Four retrospective studies report good outcome (defined as no neurological sequelae or complete resolution) in 7%, 21%, 35%, and 77%, respectively (15, 19-21). Outcome in CAGE likely depends on the amount of air involved, affected brain regions, whether or not HBOT is administered, and delay between insult and initiation of HBOT. It must be noted, though, that only few studies have adequately investigated the factors influencing outcome. A study including both arterial and venous embolism found that cardiac arrest at the time of embolism and a Simplified Acute Physiology Score II of more than 33 were the only independent predictors of mortality. Focal motor deficits or Babinski sign at the time of admission to the intensive care unit, and mechanical ventilation of more than five days were independent predictors of neurological sequelae. Furthermore, in the univariate analysis a delay between CAGE and HBOT of more than 7 h was associated with more neurological sequelae (5). This relationship between delay to HBOT and poor outcome was also demonstrated in another retrospective study (22). However, yet another study could not demonstrate an effect of delay on outcome (21).

**Difficulties and controversies**

The previous paragraphs have focused on well-known aspects of CAGE. However, many questions regarding diagnosis and treatment of CAGE are currently unanswered. This paragraph names some of these issues,
specifically the ones that were the subjects of the research presented in this thesis.

Adequate treatment requires an adequate diagnosis. Historically, CAGE is best known in the diving community, and every diver who experiences neurological dysfunction during or shortly after a dive will be regarded to have suffered CAGE until proven otherwise. Although it not always possible to confirm or reject the diagnosis of CAGE with certainty (for instance when decompression sickness is a likely alternative), most divers with neurological injury will immediately receive normobaric oxygen, followed by HBOT. In regard to diagnosis, we have therefore focused on iatrogenic CAGE, since in these patients the diagnosis is more difficult, for example because symptoms are masked by general anesthesia. This issue is addressed in chapters 4 and 5, in which we report our studies on the use of electroencephalography and regional cerebral oximetry to detect CAGE.

A second discussion in CAGE regards the optimal timing of HBOT. Several studies show that earlier treatment is associated with better outcome (5, 22), but the maximum tolerable delay is unknown. Since in almost all cases of CAGE a significant delay will be present (an exception is professional diving where a recompression facility is available on the location), it is important to gather information on the effectiveness of delayed HBOT. This could provide guidance on the amount of urgency that should be applied when a possible case of CAGE is encountered. This issue is addressed in chapter 6.

The last controversy that we will discuss here is the use of adjuvant therapy in the treatment of CAGE. A number of adjunctive treatments have been studied in an effort to improve outcome. We have focused on the most widely studied substance, intravenous lidocaine. Several animal studies have shown a positive effect of this substance on the recovery of cerebral function after CAGE (23). This effect is supposed to result from a combination of neuronal membrane stabilization, neuronal metabolism
depression, and anti-inflammatory action (24). Four human studies on the use of intravenous lidocaine as a neuroprotective agent have been performed, yielding conflicting results (25). Currently, the use of lidocaine in CAGE is neither promoted nor discouraged by the Undersea & Hyperbaric Medical Society (26). This issue is addressed in chapter 7.

Outline of this thesis

Chapter 2 provides an introductory overview of all animal models used in CAGE research, discussing their advantages and disadvantages. It provides the researcher with an overview of the factors that should be taken into account in the design of a CAGE model. This review has served as the basis for the improvements of the CAGE model presented in the remainder of the thesis.

Chapter 3 elaborates on an important issue in the use of the pig as a model for CAGE. Since the pig possesses a finely entangled network of arterioles in the carotid system proximal to the brain, direct entrance to the Circle of Willis with a microcatheter to deliver the air is not possible. Two possible ways to overcome this problem, and adequately inject air into the pig’s cerebral arteries, are presented and compared.

Chapter 4 reports the use of quantitative electroencephalography (qEEG) in quantifying the effects of CAGE on cerebral function. Several qEEG parameters are studied in the setting of acute CAGE.

Chapter 5 reports our investigation on the optimal way of peroperative detection of CAGE. We investigate two different methods to detect peroperative CAGE, namely qEEG and non-invasive regional cerebral oximetry using near-infrared spectroscopy. These methods are compared to results obtained with invasive measurement of brain oxygen tension and the cerebral microdialysis markers lactate and glycerol.
Chapter 6 presents our study on the effect of delay on the effectiveness of HBOT in CAGE. We commenced HBOT either two or four hours after induction of CAGE. Results were compared to control animals that did not receive HBOT.

Chapter 7 is a clinical study on the use of intravenous lidocaine as adjunctive treatment in neurological decompression illness (which includes CAGE and neurological decompression sickness). Divers suffering decompression illness who received HBOT and adjuvant lidocaine were retrospectively compared to a group of divers who received only HBOT.

Chapter 8 is a review study on CAGE due to hypobaric exposure. Diving related CAGE originates from pulmonary barotrauma following decompression from depth. Hypobaric activities such as flying and mountaineering also involve decompression, not from depth but from normal pressure to altitude. In this chapter all published cases that involve CAGE due to hypobaric activities are reviewed, and diagnostic and therapeutic implications are discussed.
References