Cerebral and venous (cerebral) gas embolism

A review of literature from 2005-2015

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Introduction

There is a growing interest in gas embolism as a complication of numerous invasive medical procedures. Therefore, in order to investigate the current knowledge on gas embolism we searched PubMed using the keywords (cerebral) air/gas embolism, and also consulted handbooks on diving (medicine) and textbooks on hyperbaric medicine.

Gas embolism, the entry of gas into the vascular structures, is a mainly iatrogenic problem that can result in serious morbidity and even death (Muth & Shank, 2000). The first known account of arterial embolism was by Morgagni, whose personal observations and postmortem findings were recorded in his treatise published in 1769, which was cited in the 1950s by Fries and colleagues (Fries et al., 1957). The first clinical report dates back to 1821 when Magendie described a case of venous gas embolism resulting in death (Gorman & Mitchell, 1999).

Diving

Gas embolism because of pulmonary barotrauma is an ongoing cause of concern in all types of diving operations (Edmonds, 1992). In diving, pulmonary conditions associated with bronchial obstruction are hazardous, particularly during ascent, even when all usual precautions are taken (Leitch & Green, 1986). Air embolism is the clinical manifestation of Boyle's law as it affects the lung and is the result of overdistention and rupture of the alveoli by expanding gases during ascent.

Normally, intrapulmonary and environmental pressures are equalized by exhalation during ascent. A change in pressure of approximately 70 mmHg is sufficient to cause pulmonary barotrauma (Schaefer et al., 1958; Malhotra & Wright, 1961), thus a full inspiration with compressed air at 1 m under water could, theoretically, lead to pulmonary barotrauma on return to the surface.

Threat to organs

In most cases gas embolism is in fact air embolism, although the medical use of other gases such as carbon dioxide, nitrous oxide, nitrogen and helium can also result in embolism (de la Torre et al., 1962; McGrath et al.,1989; Mitchell et al., 2000). In an experimental setting, the

effects of gas emboli differ greatly depending on whether they are venous or arterial and on the organ(s) where the emboli finally lodge (Gomes et al., 1973).

Although gas bubbles can reach any organ, occlusion of the cerebral and cardiac circulation is particularly deleterious because these systems are highly vulnerable to hypoxia. Cerebral arterial gas embolism is a severe complication which is known to occur during neurosurgical and cardiothoracic surgery as well as during many other diagnostic and therapeutic procedures

Venous gas embolism

Venous gas embolism occurs when gas enters the systemic venous system and is transported to the lungs via the pulmonary arteries. Studies on venous gas embolism have shown that filtering by the pulmonary vessels protects the systemic and coronary circulation from gas emboli orginating in the venous circulation (Butler & Hills, 1979). Animals studies have shown that when the lung filter is overloaded, the gas bubbles will break through the filter: gas doses ranging from 0.05 to 0.40 ml kg^{-1} min^{-1} were infused in dogs during ultrasonic Doppler monitoring of the arterial vessels. The pulmonary vascular filtration of venous gas infusion was complete for air doses up to 0.30 ml kg^{-1}. When the gas dose was increased to 0.35 ml kg^{-1} min^{-1} the filtration threshold was exceeded leading to arterial spillover of bubbles in 50% of the animals and increasing to 71% of the animals for a gas dose of 0.40 ml kg^{-1} min^{-1} (Butler & Hills, 1985; Butler et al., 1995). A similar study in pigs resulted in a 130% increase of pulmonary arterial pressure to 40 mmHg: the breakdown incidence of bubbles was 67% with an air flow of 0.10 ml kg^{-1} min^{-1} (Vik et al., 1990). Comparison of these data suggests that the threshold value for the breakthrough of gas bubbles in pigs is less than in dogs. This difference was explained haemodynamically, whereby the rise in pulmonary pressure accompanied by a dramatic drop on the arterial side of the circulation may increase shunting via arteriovenous anastomosis (Vik et al., 1990).

Entrapment

Venous gas embolism may lead to trapping of gas bubbles in the pulmonary capillary bed, which can lead to decreased gas exchange (Bove et al., 1974), cardiac arrhythmia (Evans et al., 1981; van Blankenstein et al., 1997), pulmonary hypertension (Evans et al., 1981), right

ventricular strain (Durant et al., 1949; van Blankenstein et al., 1993, 1994), cardiac failure (Durant et al., 1949) and arterial gas embolism because of shunting to the left systemic vascular system (Butler & Hills, 1985).

Entrapment of venous bubbles in the pulmonary microcirculation may also lead to cellular injury and lung oedema resulting from the release of vasoactive mediators following pulmonary vascular obstruction (Flick et al., 1981, 1983; Ohkuda et al., 1981; Albertine et al., 1984; Wang et al., 1992). This type of lung injury is thought to be mediated by activated neutrophils sequestered in the pulmonary capillary bed during gas embolism.

The activated neutrophils release thromboxane and leukotrienes that increase alveolo-capillary permeability resulting in oedema.The capillary leakage will result in a dose-dependent inactivation of endogenous surfactant (Lachmann et al., 1994) leading to alveolar collapse, formation of atelectasis, impaired gas exchange and, thus, the need for mechanical ventilation.

Clinical occurrence

Venous gas emboli most often occur in patients during the insertion, maintenance or removal of a central venous catheter (Halliday et al., 1994; Palmon et al., 1997). In a review of the literature, Heckmann and colleagues discussed 26 cases in which most venous gas emboli occurred during a subclavian or jugular vein catheterization procedure (Heckman et al., 2000). Embolism can also occur as a result of lung trauma induced by mechanical ventilation (Marini & Culver, 1989; Ho & Ling 1999). Bricker and colleagues used transoesophageal echocardiography in patients who required mechanical ventilation with positive end-expiratory pressure (PEEP) and found continuous venous gas embolism in five of the eight lung trauma patients (Bricker et al., 1994); they concluded that there is a relatively high occurrence of venous gas embolism in patients with pulmonary barotraumas associated with increased ventilatory pressures, and that venous emboli may contribute to cardiovascular instability and may exacerbate lung injury in critically ill patients. In gynaecological surgical and diagnostic procedures, venous gas embolism is a rare and unexpected complication (Mushkat et al., 1995; Weissman et al., 1996). Laparoscopy using carbon dioxide can also lead to a venous CO2 embolism (McGrath et al., 1989). Finally,

during neurosurgery air may enter the veins, especially when patients are in the sitting position (Porter et al., 1999).

Paradoxical emboli

In principle, every venous gas embolism has the potential to develop into an arterial gas embolism; when this happens it is called a paradoxical embolism (Black et al., 1991). A paradoxical embolism occurs when the filter capacity for gas bubbles of the pulmonary capillary bed is exceeded and gas bubbles shunt from the venous side to the arterial side of the circulation. Transcardiac passage of venous gas bubbles can also occur in the presence of any right to left shunt, including a patent foramen ovale (Fraker, 1979) and more recently discussed the presence of shunting in the pulmonary vasculature (Wilmhurst, 2015). The application of PEEP during mechanical ventilation (Jaffe et al., 1991), Valsalva manoeuvres (Chen et al., 1992) and coughing (Dubourg et al., 1984) can increase the interatrial movement of bubbles in patients with atrial shunts.

Cerebral gas embolism

Cerebral gas embolism is a serious hazard: when bubbles occlude the brain vasculature, intracranial pressure (ICP) increases (de la Torre et al., 1962) and an extremely inhomogeneous distribution of blood flow in the brain causes hyperaemia and ischaemia (Hossman & Fritz, 1978; Fritz & Hossman, 1979; Hossmann, 1998; Williams et al., 2001). The pathophysiology of CAGE mainly depends on the air bubble size. Microbubbles 'irritate' the vascular wall leading to an instantaneous breakdown of the blood–brain barrier (Johansson,1980); on the other hand, these tiny bubbles are rapidly absorbed and may only briefly interrupt cerebral arteriolar flow (Gorman & Browning, 1986). A good correlation has been found between cerebral blood flow and brain function after gas embolism by small bubbles at a maximum size of 250 um (Hossman & Fritz, 1978; Dutka et al., 1987; Helps et al., 1990b). The passage of a gas bubble will obstruct local blood flow, but flow will normalize after disappearance of the bubbles. However, normalization is often only temporary and blood flow may subsequently decrease to levels below those required to maintain neuronal function and survival (Meldrum et al., 1971; Helps et al., 1990a, b). An explanation for this mechanism was suggested by Dexter and colleagues who calculated that the absorption of large gas emboli may take several hours, which is long enough to cause

primary ischaemic injury with diffuse brain oedema leading to raised ICP (Dexter & Hindman, 1997). This latter finding was confirmed by our group in an experimental study showing that after a large gas embolism ICP increased from 12 to 52 mmHg within 2 h after embolization with severe detrimental effects on brain oxygenation and glucose metabolism (van Hulst et al., 2003).

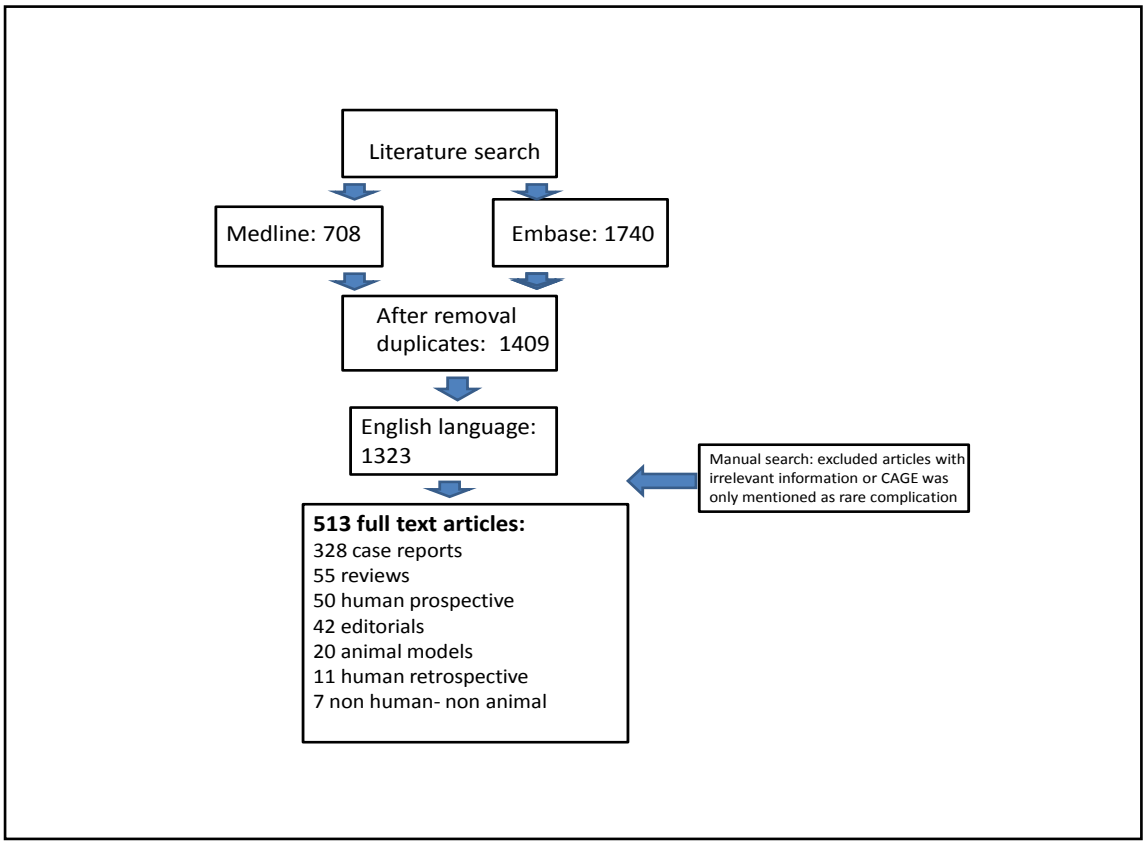
Method

In order to get an overview of all literature since the ECHM meeting in 2004, we did a search in Medline and Embase for relevant studies. The search was performed in September 2015. Search results were limited to studies written in English and published since 2004. Articles were initially selected based on title and abstract, after which the fulltext article was read to confirm article relevance. References of included papers were checked to identify additional articles. In total, this search strategy resulted in 1323 studies of CAGE . Original search showed 708 studies in Medline and 1740 in Embase database, after removal duplicates 1409 studies were left. Other languages were excluded which left 1323 studies. In addition, we performed a manual search on relevant publications in this 1323 studies and excluded publications without relevant titles or/and abstracts and those where (cerebral) air embolism is mentioned as a rare complication of medical procedures or interventions. Finally, we ended up with 513 papers

These studies were divided into the following groups:

Animal studies orginal work:	20
Case reports:	328
Editorials/correspondence:	42
Human prospective:	50
Human retrospective:	11
Non human/non animal models:	7
Reviews:	55

We, as authors decided to run through the animal studies, human prospective and human retrospective studies and to exclude case reports, editorials and reviews in order to gain new scientific information.



Results

In the series of animal models (n=20), new models are described as well as therapeutic interventions on different animals have been applied. As gas embolism is still an important topic in cardiac/thoracic surgery, new techniques to decrease intravascular bubbles are validated. Most of these studies are important for cardio-thoracic anesthesiologist and surgeons but this information is less useful for this overview.

De Lange (2008) applied PFC (perfluoro carbons) in rats during cardiopulmonary bypass as a therapeutic measurement but failed to demonstrate a positive effect. Eckmann (2013) used prophylactic surfactant in rats which rendered stroke undetectable by MRI scanning and markedly reduced the postembolic deficits in both cognitive and sensorimotor performance in treated rats, with normalization of motoric function and tactile tests within 7 days.

Havnes (2010) used S100B as a neuromarker in rats who suffered decompression sickness and found a correlation between bubbles scores by Doppler and the level of S100B. A series of studies in pigs by Weenink et al. demonstrated that NIRS (non-invasively measured cerebral oxygen saturation) can detect the local effects of air emboli on cerebral oxygenation, but with reduced sensitivity as compared to intra parenchymal oxygen tension

(2014). This group also showed that qEEG (quantitative electroencephalography) is a useful non-invasive method to diagnose and monitor CAE in pigs (2012).
However in another publication, they were not able to demonstrate an effect of hyperbaric oxygenation on cerebral function after a delay of 2 or 4 hours (2013). The injury caused in this pig model could be too severe for a single session of hyperbaric oxygenation to be effective. They concluded that this study should not change current hyperbaric oxygenation strategies for cerebral arterial gas embolism, but further research is necessary to elucidate our results. Whether less severe injury benefits from hyperbaric oxygenation should be investigated in models using smaller amounts of air and clinical outcome measures.
Yeniguen (2012) concluded on findings in a rat model that neurological side effects of cerebral gas embolism depend on the total volume of embolised air but not on the size of the bubbles. These results may have further impact for clinical protection of cerebral air microembolisation.

In the series of human retrospective studies (n=11) most of the publications involved are on cardiothoracic and neurosurgical patient series and described the incidence of (cerebral) gas embolism or the techniques to detect intravascular bubbles during surgery (TCD, ETCO2). The incidence of gas embolism in most of the studies is low (0.08-1.4%). There were no studies on divers with decompression illness or AGE.
One study describes a retrospective series of clinical patients (n=36) with iatrogenic CAGE treated with HBO (Tekle 2012). A total of 26 (72%) of the 36 patients had favorable outcome. Cardiopulmonary symptoms associated with CAGE were significantly more common in venous source of gas compared to arterial but did not influence the rate of favorable outcomes. Young age and time-to-HBO < 6 hours were associated with higher rate of favorable outcome. Timely diagnosis and differentiation from thrombo-embolic ischemic events is an important determinant of successful HBO (Gao, Wu et al. 2009, Bessereau, Genotelle et al. 2010, Honek, Sramek et al. 2014, Barak, Madden et al. 2015) treatment.

In the series of human prospective studies (n=50), again most of the publications presented results from effects of bubble filters or other techniques to minimize bubbles in the ECMO, incidence of air embolism in cardiac, cardiopulmonary resuscitation and neurosurgical procedures.

Bessereau (2010) presented a study of 125 iatrogenic air embolism treated with HBO in the hospital in 12 years. Cardiac arrest at time of accident and ICU admission, and SAPS II of 33 or more were independent prognostic factors of 1-year mortality. Among ICU survivors, independent predictors of 1-year mortality were age, Babinski sign and acute kidney failure. Focal motor deficits and Babinski sign on ICU admission, and duration of mechanical ventilation of 5 days or more were independent predictors of long-term sequels.
There were 3 studies on divers in this series. Barak (2015) showed in a group of 20 PFO negative divers after a no-deco dive followed by moderate exercise that bubbles can pass the lungs via intra-pulmonary AV anastomoses into the arterial circulation. Gao (2009) used MRI in 7 divers treated for CAGE to show abnormalities in the brain: both cortical grey matter and subcortical white matter can be affected and the cerebellum is also the target of air embolism. They mentioned that the MRI of brain is a sensitive method for detecting cerebral lesions in compressed air divers in diving accidents and should be finished on divers in diving accidents within 5 days. Honek (2014) demonstrate the effect of catheterbased PFO closure on the occurrence of post-dive arterial bubbles in a group of 20 divers. After closure of the PFO, the divers made dives to 18 and 50 mt and no arterial bubbles in the left heart chambers in this divers with a PFO closure device were shown.

Discussion

There is still a striking lack of good studies on diagnosis, treatment and after-care of patients with air embolism. This includes venous as well arterial gas embolism in both clinical patients and in divers. Treatment tables are the commonly used USN, Royal Navy and French tables but also with an impressive variety of modifications with air, oxygen and helium as a treatment gas. Studies on adjunctive therapy, eg aspirin, lidocaine etc are anecdotal or case reports and in the best situation with small numbers and underpowered.
There is a need for international multicenter studies on patients with air embolism on the whole field of diagnosis, hyperbaric and drug treatment and follow-up.

WE RECOMMEND (proposed by authors, to be discussed)

1. Hyperbaric therapy is recommended in cases of arterial and venous gas embolism with neurological or/and cardiological manifestations. A short interval (< 6 hr) between embolism and hyperbaric treatment is associated with a better outcome. However, response to hyperbaric treatment with substantial clinical improvement has been observed in many case reports and small series of patients after 24 hrs or more.
   Level 1 recommendation , Grade B (moderate level of evidence)

2. Administration of 100% oxygen in the acute phase results in resolving signs/symptoms in some patients but because secondary deterioration can occur later, hyperbaric oxygen therapy is still recommended.
   Level 1 recommendation, Grade B (moderate level of evidence)

3. There is no good evidence for recommending deep treatment tables (>4.0 bar/30 mt). Consideration of the use of heliox or nitrox at deeper depths must be undertaken by each unit based on experience and logistic arguments
   Level 2 recommendation, Grade B (moderate level of evidence)

4. Adjunctive therapy for isolated AGE includes:

Lidocaine	Level 2, level of evidence B.
Aspirine, NSAID's	Level 3, level of evidence B.
Anticoagulants	Level 3, level of evidence C.
Corticosteroids	No recommendation

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