Declaration of interest

None declared.

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EDITORIAL II

Retrograde cerebral venous gas embolism: are we missing too many cases?

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Air embolism is a well-known adverse event of medical therapy. The epidemiology, pathophysiology, and management is well understood and described.[1] Cerebral gas/air embolism (CGE) on the other hand is thought to be uncommon and the average anaesthetist/intensivist currently may see only a few or none in a life time. The common error is to misdiagnose it as a thrombotic or thrombo-embolic stroke.[2] It may arise in a patient who has survived a significant systemic air/gas embolism event, with or without a need for cardiopulmonary resuscitation (CPR). It may however be more subtle or even unnoticed in an unconscious or anaesthetized patient or in situations where slow entrainment of small amounts of air takes place over a period of time. Reviewing the literature has raised a significant patient safety issue due to missed or delayed diagnoses, but also an interesting new understanding of the mechanism in some cases.[3]

Hyperbaric physicians generally have a higher index of suspicion because of training in decompression-related accidents and the occasional referral of iatrogenic CGE for hyperbaric oxygen therapy (HBO). Looking at the hyperbaric medicine literature, a significant discrepancy is seen between the number of iatrogenic CGE cases referred for HBO in the UK and France or Australia.

In the UK, only five cases were treated with HBO in the last 10 yr according to British Hyperbaric Association (BHA) treatment database (J. Sayer, personal communication, 2013). A further seven cases were referred and discussed but not accepted for treatment because they had mainly too advanced damage to benefit from HBO. In Sydney, eight cases were treated over 10 yr[4] and the total for Australia was 39 cases reported over 10 yr.[5] In Marseille, 86 cases were treated in a 20 yr period[6] and in Paris 125 cases in 10 yr (Fig. 1).[7] When asked about the high incidence in France, the explanation was given of a high-profile case that was initially missed, with a bad outcome, which soon focused the attention of French Clinicians (D. Annane, personal communication, 2013).

One of the reasons for a lower rate of reporting in the UK could be lack of belief in hyperbaric therapy. However, several retrospective series show good outcome if referred early, and 6–7 h seem to be the target.[7 8] However, there are case reports of dramatic improvement, if not full recovery, up to 60 h after onset.[9 10]

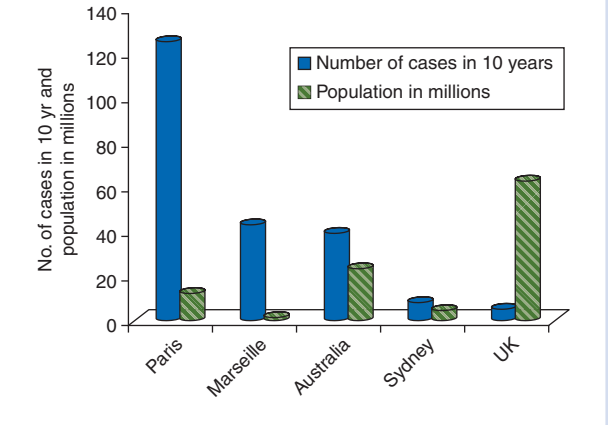

Fig 1 Illustration of the significantly lower incidence of CGE cases treated with HBO in the UK compared with France and Australia.

Finding non-HBO data sources of cerebral gas embolism in the UK has been impossible. As a substitute, we were looking for data about air embolism in general and found the Case Mix Programme (CMP) of the Intensive Care National Audit and Research Centre (ICNARC) useful. On request, they reported 4.5 cases per 100 000 intensive care unit admissions, or six cases per year with an admission diagnosis of venous air embolus, arterial air embolus, or both.[11] The National Reporting and Learning System (NRLS) of the National Patient Safety Agency (NPSA) reported 11 cases of air embolism between June 2009 and June 2011.[12] Neither of these sources indicated whether the patients had systemic only or cerebral involvement, nor did they indicate what the final outcome was.

Distance from suitable hyperbaric units could deter clinicians from referring cases. Early referral is essential and helicopter transfer would be the solution to save lives and brains if distance is a problem.[6]

The CGE related to intravascular line accidents has been classified as a 'NEVER EVENT' with associated penalties, which makes acknowledgement unattractive. This may be true in the USA,[13] but in the UK, it seems most clinicians are not aware of this new 'status' of CGE.

It is important to remember that CGE can present exactly the same as other types of stroke. If the patient is outside the window of thrombolysis or has a contraindication to thrombolysis, imaging will in many instances be delayed as it would not affect the management. This may allow bubbles to disappear in some cases and could potentially be deliberately delayed for cynical reasons and should not be tolerated, but will be difficult to prove.

It is possible that the seriousness and the pathophysiology of cerebral venous gas embolism (CVGE) is under-estimated, because it is a new concept and not yet adequately described in acute medicine literature.[3 14] This theory arose when two cases were discussed with the HBO team. They deteriorated unexpectedly after initial mild symptoms and it was felt that the patients would not benefit from escalating treatment as both these patients had severe cerebral oedema and irreversible damage at that stage.

What is CVGE?

The term 'retrograde cerebral venous gas embolism' explains exactly what it is. We selected the abbreviation 'CVGE' to differentiate it from the already accepted 'CAGE' for cerebral arterial gas embolism.

The concept of 'retrograde passage of air bubbles' is a fascinating new understanding of an old phenomenon, first described in a letter to the editor of *Lancet*.[15] Subsequently, a laboratory model has demonstrated how this could happen, depending on flow dynamics, buoyancy depending on bubble size, and position of the thorax relative to the bed.[3 16]

This has introduced a new facet into understanding CGE. This is a field that is already difficult to study because of its apparent rarity and the inability to find a suitable laboratory model to assess different therapeutic modalities. The traditional concept of the first two of the following mechanisms as the only causes of CGE is now clearly challenged:

(i) Direct injection of gas into the arterial system during angiography. Pulmonary barotrauma allowing gas to enter the pulmonary veins, then via the left heart to the systemic arterial system, including the coronary and cerebral arteries.

(ii) Paradoxically, from the venous system through an intracardiac right-to-left shunt,[1] or where an intracardiac shunt is excluded, arteriovenous malformations in the lungs or overwhelming of the pulmonary capillary filter mechanism have been demonstrated to allow gas to enter the systemic arterial system.[17]

(iii) The concept of CVGE should be recognized as a third generic mechanism of cerebral gas embolism. A review of previous case reports of CGE has demonstrated several cases originally reported to be CAGE, to be actually retrograde CVGE.[3] A further interesting finding has been the discovery of CVGE in certain cases after CPR.[18] In some of these cases, insertion of peripheral or central lines could be implicated. In others, pulmonary trauma with air entering the circulation may explain it. However, those who have CVGE obviously were due to retrograde flow. This may implicate a low cardiac output state allowing retrograde flow of bubbles either in the supine CPR position or more likely from the thoracic compressions.

How do we deal with this newly gained information?

Prevention of harm is the first priority

The traditional view of central lines, neurosurgery in the sitting position, and cardiopulmonary bypass procedures being the main culprits has changed significantly. Numerous endoscopy, angiography, tissue biopsy, minimally invasive surgery techniques, and peripheral venous access, has been shown to cause

venous gas embolism[1 19] and possibly CVGE as well. Prevention is obviously the primary aim and anaesthetists have a paramount preventive role to play when considering intravascular devices, various surgical procedures, and monitoring of patients during such procedures.[20] Our secondary aim is to diagnose and treat all adverse events promptly. We should have a high index of suspicion whenever a patient develops a peri-procedural neurological event. Depending on the patient's condition, potential delays in imaging may necessitate urgent hyperbaric therapy without imaging if the clinical circumstances are convincing.

How do we treat CVGE?

At this point in time, nobody knows what the best therapy is, except of course the normal ABCs and supportive care. It is essential to realize that it is a potentially lethal condition.[16 21 22] HBO for CVGE has been described in two cases only.[21 23] The latter survived,[23] but the former did not.[21] The course and management of the case in the former report is very sketchy and difficult to get a good picture, but a couple of case reports do not help us to select a course of treatment in a devastating condition. Patients with decompression illness (DCI) have bubble-induced injury which has been treated with HBO for many decades. Numerous series of timely and successful HBO for CAGE has also been described.[4–7] Although 50% (n=2) of cases with CVGE did not respond to HBO,[21] there is no reason to believe that the CVGE cases will not benefit as much as CAGE. Diligent observation and reporting of all cases with CVGE is required to obtain a better idea about the incidence, pathophysiology, and outcome.

How do we investigate it further?

Any study randomizing patients with DCI or CAGE to therapy without HBO would be unethical.[24] The same probably applies to CVGE. No suitable laboratory model could be created yet.[24] Using a porcine model to study injuries to the heart or several other systems seems practical, but to study injuries to the porcine brain seems irrational as the human brain has so many functions that cannot be assessed in an animal model.[25] That leaves case reports (remembering that a case report flagged up the first case!)[15] and the compilation of a CVGE register. Hopefully, this editorial can generate interest in a national or even international collaboration in a case series.

Anaesthetists are still often involved in resuscitation or stabilization of patients that might potentially suffer from air embolism and a high index of suspicion of CGE will help with diagnosis. When such patients are booked for imaging, the urgency of making the diagnosis should be emphasized to radiology departments. The need to differentiate between cerebral arterial and cerebral venous embolism should also be explained. It is noteworthy though that many experts encourage urgent referral for HBO, if immediate imaging is not available.[7]

Cases of confirmed CVGE should also be submitted for publication as case reports, with particular emphasis on the possible mechanism of the accident, management, and short- and long-term outcome. In addition to that, submission of anonymized detail to the Cerebral Gas Embolism Registry (http://www.gasembolism.org.uk/) will hopefully in due time help with the understanding of the real incidence, best management approach, and expected outcome.

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ICNARC collected data

These data derive from the Case Mix Programme Database. The Case Mix Programme is the national, comparative audit of patient outcomes from adult critical care coordinated by the Intensive Care National Audit & Research Centre (ICNARC). These analyses are based on data for 133 425 admissions to 205 adult, general critical care units based in NHS hospitals geographically spread across England and Wales. For more information on the representativeness and quality of these data, contact ICNARC.

Declaration of interest

None declared.

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EDITORIAL III

Fluid management in association with neonatal surgery: even tiny guys need their salt

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The practice of giving i.v. fluids as part of routine paediatric care was established during the 1950s, and important initial questions to answer were what type of solution to give and at what infusion rates. In 1957, Holliday and Seger[1] published a seminal manuscript, recommending the well-known '4-2-1 rule', which almost immediately was adopted as a worldwide standard. The composition of a normal i.v. maintenance fluid was however somewhat more difficult to determine but was heavily influenced by the composition of normal breast milk, which has a sodium content in the range of 10–40 mmol litre^{-1}.[2] Thus, effectively hypotonic glucose solutions with a low sodium content came into wide-spread use maybe best exemplified by the British 4% glucose 0.18% sodium ('four and a fifth').[3] The history since the 1950s has shown that the approach described above works sufficiently well in the vast number of routine paediatric cases.

However, using the standard Holliday and Segar volume recommendations paired together with the use of an i.v. solution with a sodium concentration that diverges substantially from that of the extracellular fluid does become a problem in a situation of a neuroendocrine stress response, either provoked by surgery or significant medical illness. The reason for this is that the stress response includes a substantially increased secretion of anti-diuretic hormone (ADH) that will result in retention of free water. A physiologically more appropriate approach during these circumstances is to use a solution with a close to physiological concentration of sodium (120–140 mmol litre^{-1}) combined with the administration of a reduced infusion volume compared with the normal situation (50–70% of normal infusion rate).[4 5] If not adhering to a more physiological approach, the stage is set for dilutional hyopnatraemia that can be life-threatening or even fatal.[6–11]

The insight that the paediatric use of i.v. low sodium solutions was unsuitable in the context of a stress response and that a sodium content closer to that of extracellular fluid is more appropriate was published as early as 1964.[12] However, since no appropriate i.v. solutions were commercially made readily available by the manufacturers, the regimen of using effectively hypotonic solutions in association with paediatric anaesthesia and surgery has continued in many centres even to this day. A questionnaire-based study from 2001 reported that 97% of UK-based anaesthetists routinely used effectively hypotonic i.v. solution intraoperatively in children.[13] A similar study published in 2006, also surveying the UK practice,