Cerebral gas embolism associated with central venous catheter: Systematic review

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1. Introduction

Cerebral gas embolism (CGE) is a known complication of several medical procedures during which air enters the vascular structures. Air embolism may occur in circumstances such as venous catheterization, neurosurgical, vascular and cardiac surgeries, gastroenterology procedures, pulmonary barotrauma and invasive lung procedures (1). The use of central venous catheters (CVCs) in settings outside the intensive care unit, namely in awake and ambulatory patients, increases the risk of accidental catheter disconnection and manipulation by undertrained personnel. However, reports of CGE associated with CVCs in the medical literature are not frequent and largely confined to single case reports, which may be explained by the perception of physicians that this should be a “never event” and possible lack of recognition of clinical and imaging characteristics (2). CGE associated with CVCs may involve the cerebral arterial vasculature (for which to occur, a right-to-left shunt, even if transient, must exist) or may involve the cerebral venous vasculature by a retrograde mechanism where air ascends through the jugular vein opposite to blood flow (2). Although CGE may be formally considered as an acute stroke according to the World Health Organization definition, neurological manifestations of CGE may be mild and transient or accompanied by a severe disturbance of consciousness, and physiopathology may include mechanisms other than central nervous system infarction or ischemia. The current systematic review aims to describe manifestations and imaging findings of CGE patients associated with CVCs and to find clinical predictors of mortality.

2. Materials and methods

2.1. Local cases

Our Neurology Department database for hospitalized patients between January 2008 and May 2015 was reviewed to select patients...
with CGE associated with CVCs. Clinical characteristics, imaging findings, treatment and outcome were collected from patient records.

2.2. Literature search

Pubmed search in May 2015, for the following search terms: “air embolism” or “gas embolism” in combination with “catheter” or “line”. Articles written in English, French, German, Portuguese, Spanish and Norwegian were included. Selection of all papers reporting patients with air embolism thought to be associated with a CVC, either presumed by clinical manifestations and circumstances or confirmed by diagnostic tests, with manifestations that could be attributed cerebral dysfunction or with imaging evidence of cerebral air embolism. Reference list of the papers of interest were also reviewed according to this selection criteria. Papers reporting case series of patients with CGE associated with CVCs were included in the descriptive analysis but excluded from the analysis of mortality prediction if individualized data for single patients could not be retrieved. Patients found in our database have not been previously reported and were included in the analysis. Conference proceedings and papers without retrievable information concerning clinical manifestations were excluded.

2.3. Statistical analysis

Descriptive analysis, Pearson’s chi-square test, Fisher’s exact test and Mann–Whitney U test were used according to variables types and test assumptions. Univariate binary logistic regression was used for analysis of predictors of mortality, and odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. IBM SPSS 22 ® with an alpha value set at 0.05 as the statistical threshold for significance.

3. Results

We found 4 patients with CGE associated with CVCs in our database, details can be found in the Supplemental Material. Imaging findings of local cases 1–3 are illustrated in Fig. 1.

Pubmed search originated 899 papers, final selection included 66 papers of interest, with inclusion of 158 patients who met selection criteria, of which 4 patients are previously unreported local cases (Fig. 2).

The majority of papers (n = 57) reported single patients. Neurological manifestations of the acute event were available for 158 patients (100%), body position on symptom onset was available for 48 patients (30.4%), computed tomography (CT) was performed in 68 (43.0%) and magnetic resonance imaging (MRI) in 24 patients (15.2%). No reference to treatment was available for 17 patients (10.8%). In one paper, clinical characteristics and outcomes could be obtained, but data was not individually reported for each patient (3). This paper and another paper (4), in which no outcome was reported, were included in the descriptive analysis, but excluded from the mortality analysis. Details of the 158 patients included in this systematic review are provided in Supplemental Digital Content, with accompanying references.

3.1. Descriptive analysis

Mean age was 56.4 years and 71.8% of patients were male. CGE occurred after accidental CVC disconnection or leak in 88 patients (61.5%), after CVC removal in 31 (21.7%), after CVC insertion in 10 (7.0%), after CVC manipulation in 10 (7.0%) and with no apparent relation with CVC procedure in 4 (2.8%). Symptom onset occurred in the upright position (standing or sitting upright) in 77.1% and in recumbent position in 22.9%. Median time from CVC event to symptom onset was during the first minute (interquartile range 1–7.5; data available for 37 patients). The most frequent neurological manifestation was sudden...
onset focal neurological sign (n = 107, 67.7%), followed by coma (n = 94, 59.5%), epileptic seizures (n = 39, 24.7%), encephalopathy (n = 34, 21.5%) and headache (n = 9, 5.7%). Head CT revealed intracranial air bubbles in 47/68 patients (69.1%): the most common localizations of intracranial air emboli were the subarachnoid space (n = 26) and cerebral parenchyma (n = 23), followed by venous sinus (n = 13), and no information concerning air distribution was available for 6 patients. Air bubbles located exclusively in intracranial venous sinus were found in only 3 patients. Brain MRI findings were reported for 23 patients: only 3 had normal imaging, recent ischemic lesions were reported in 18 patients and edema was reported in 6 patients. Of note, diffusion weighted imaging (DWI) was performed in only 14 patients. Ischemic or edematous lesions were found in 48/72 patients who underwent imaging or pathological diagnosis, and the most frequent localization was in the right hemisphere (n = 44) and the frontal lobe (n = 35). In the majority of cases there was no reference to shunt investigation (n = 106), cardiac shunt was diagnosed in 11 patients and pulmonary shunt was reported in 3 patients. The most commonly reported treatments used were hyperbaric oxygen therapy (n = 88, 62.4%), high flow oxygen (n = 27, 19.1%), Trendelenburg positioning (n = 10, 7.1%) and anticonvulsant (n = 10, 7.1%). Other treatment options such as CVC aspiration, intravenous thrombolysis, anticoagulation, steroids, mannitol and intravenous lignocaine were less frequently reported. Autopsy results were reported in 6 patients (5–10), and neuropathological findings were described in 4 patients, which included cerebral ischemic lesions (n = 4), cerebral hemorrhagic lesions (n = 1), and findings suggestive of air embolism such as clear cavities in the cerebral parenchyma (n = 1) and choroid plexus vessel dilation with clear lumen (n = 1).

3.2. Mortality analysis

Outcome was reported in 157 patients, and mortality during the acute phase occurred in 34 patients (21.7%), at a median of 3 days after the onset of clinical manifestations of CGE. Among the 123 patients who survived the acute phase, follow-up information concerning clinical status was available for 69 patients, of which 28 (40.6%) recovered completely and 4 (5.8%) died after hospital discharge (range between 5 weeks and 7 months after CGE). Characteristics of patients according to survival during the acute phase, excluding references 3 and 4, are described in Table 1 (n = 107).

Predictors of mortality in univariate analysis included increasing age (OR = 1.06, 95%CI = 1.03–1.09, p < 0.001), male sex (OR = 3.5, 95%CI = 1.09–11.23, p = 0.035), coma (OR = 5.09, 95%CI = 2.00–12.97, p = 0.001) and cardiorenal failure shortly after symptom onset (OR = 18.42, 95%CI = 3.72–91.30, p < 0.001). There was a trend for association of mortality and presence of air bubbles in CT (OR = 3.86, 95%CI = 0.99–15.00, p = 0.051) and presence of any cerebral lesion secondary to gas embolism (OR = 2.85, 95%CI = 0.84–9.72, p = 0.094).

4. Discussion

This systematic review demonstrates that clinical manifestations of acute CGE associated with CVCs may mimic acute ischemic stroke, but major differences include the frequent occurrence of a severe consciousness disturbance and epileptic seizures. A high level of suspicion for CGE is needed in patients with CVCs who present with sudden-onset cardiorespiratory instability, focal neurological signs, decreased vigilance and seizures. The most useful imaging technique is CT, which detected intracranial air bubbles in 2/3 of patients with the clinical diagnosis of CGE, especially when performed in the hyperacute phase.

Air bubbles were more frequently located in the vascular structures of the subarachnoid space, which is interpreted by some authors as intra-arterial (11) and by others as intra-venous (5). Given the sudden onset of symptoms in the majority of cases and the severity of the neurological manifestations, we favor the hypothesis of paradoxical arterial gas embolism, not venous gas embolism, as the most frequent form of CGE associated with CVCs. A cardiac or pulmonary shunt was found in only 14 patients in this systematic review, but interpretation is limited because reference to shunt investigation was absent in the majority of papers. Additionally, arterial gas embolism associated with CVCs in the absence of an anatomical pulmonary or cardiac shunt in autopsy has been demonstrated to be possible (12). Experimental animal models of cerebral arterial gas embolism show that after injection of air into the internal carotid artery, a significant increase in intracranial pressure occurs, which is accompanied by a significant decrease in cerebral perfusion pressure and brain tissue oxygenation (13). Retrograde gas embolism through the internal jugular vein to intracranial venous sinus has been considered by Bothma and Schlimp (2) as possibly underestimated in acute medicine literature, but was demonstrated to be possible in experimental simulations (14), and air in intracranial venous sinus was found in 13/68 patients in this systematic review. Right hemisphere predominance of ischemic/edematous lesions in CGE does not settle the discussion whether embolism is mainly arterial (paradoxical) or venous (retrograde), because right brachiocephalic artery or vein, respectively, would be the first vascular structure encountered in each mechanism of gas embolism. Therefore, cerebral lesions induced by CGE may be: 1) ischemic due to interruption of cerebral arterial flow, which is supported by the finding of cytotoxic edema in DWI (15); 2) ischemic due to blood flow change in intracranial venous sinus or cortical veins, promoting vasogenic edema and venous infarctions; 3) inflammatory due to breakdown of blood–brain barrier and activation of immune...
neuropathological and structural damage to the endothelium, which may lead to microvascular dysfunction, platelet and leucocyte adhesion, protein activation and precipitation of vasogenic edema without recent ischemic lesions in DWI in case 3 (17).

It has been demonstrated that air emboli may be caused by CVC manipulations, and these findings were observed in two cases (17). In another case (17), it has been demonstrated that air emboli may induce platelet and leucocyte adhesion, protein activation and precipitation of vasogenic edema without recent ischemic lesions in DWI in case 3 (17).

Table 1

<table>
<thead>
<tr>
<th>Characteristics of patients with cerebral gas embolism according to survival.</th>
<th>Survival</th>
<th>Death</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>44 (61.1%)</td>
<td>22 (84.6%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Age</td>
<td>56.0 (40.5–67.5)</td>
<td>72.5 (62.0–80.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVC insertion/removal/manipulation</td>
<td>30 (45.5%)</td>
<td>11 (42.3%)</td>
<td>0.785</td>
</tr>
<tr>
<td>Accidental CVC disconnection/CVC leak</td>
<td>33 (50.0%)</td>
<td>13 (50.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Recumbent position</td>
<td>6 (19.4%)</td>
<td>5 (29.4%)</td>
<td>0.486</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory dysfunction</td>
<td>42 (58.3%)</td>
<td>17 (58.6%)</td>
<td>0.979</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>28 (38.9%)</td>
<td>12 (41.4%)</td>
<td>0.817</td>
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<tr>
<td>Headache</td>
<td>9 (11.7%)</td>
<td>0</td>
<td>0.050</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td>55 (71.4%)</td>
<td>6 (53.3%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Seizures</td>
<td>22 (28.6%)</td>
<td>10 (31.3%)</td>
<td>0.620</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>26 (33.8%)</td>
<td>8 (26.7%)</td>
<td>0.479</td>
</tr>
<tr>
<td>Coma</td>
<td>27 (35.1%)</td>
<td>22 (73.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
<td>2 (2.8%)</td>
<td>10 (34.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Imaging findings</td>
<td></td>
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<td></td>
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<tr>
<td>Intracranial air bubbles</td>
<td>28 (60.9%)</td>
<td>18 (85.7%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Any cerebral lesion secondary to gas embolism</td>
<td>30 (61.2%)</td>
<td>18 (81.8%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High flow oxygen</td>
<td>23 (28.6%)</td>
<td>8 (26.7%)</td>
<td>0.722</td>
</tr>
<tr>
<td>Hyperbaric oxygen therapy</td>
<td>31 (40.3%)</td>
<td>7 (23.3%)</td>
<td>0.100</td>
</tr>
</tbody>
</table>

CVC: central venous catheter. Age in years: median (interquartile range).

a Mann–Whitney U test.

b Fisher’s exact test.

c Hypodense lesions in computed tomography or hyper/hypointense lesions in magnetic resonance which were interpreted as a consequence of cerebral gas embolism.

d Continuous variables were compared by t test, non-parametric variables by Wilcoxon test.

5. Conclusions

CGE associated with CVCs may be a catastrophic event and is associated with a high mortality, thus, prevention should be a priority in a medical era in which intravascular procedures and devices are frequently used in hospital settings (21). Judicious use of CVCs, regular training of health professionals who are required to manipulate CVCs, and clinical protocols for catheter selection, insertion, removal and manipulation may all help to prevent this severe complication.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2016.01.043.

Conflicts of interest

None.

References


