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# Air Embolism Complications Associated with Sclerotherapy.

## *Les complications liées aux embolies gazeuses secondaires à la sclérothérapie.*

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### *Summary*

**Introduction:** Since injection of air is an inherent part of foam sclerotherapy, any correlation between the presence of patent foramen ovale (PFO) and neurological complications due to air embolisms would be important in understanding the risks of air embolisms and how to treat them when they occur in conjunction with sclerotherapy.

**Methods:** An analysis of published reports of neurological events and disturbances after liquid sclerotherapy (LS) or foam sclerotherapy (FS) was conducted following a search of PubMed, Ovide Embase, Medline, Medscape, and Google Scholar databases.

**Results:** Eleven cases of suspected air embolism following FS were published between 2006 and 2011.

Three cases were diagnosed as transient ischemic attacks, and the remaining 8 cases were diagnosed as strokes.

These cases were typically associated with paradoxical arterial embolisms of the middle cerebral artery or ventricular artery, and PFOs were identified in 8 of the 11 cases. Six cases of suspected air embolism following LS were published between 1947 and 2006; stroke was diagnosed in 4 cases, and transient ischemic attack was diagnosed in the remaining 2 cases.

While PFO was identified in only 2 of the 6 cases, the data reporting for LS neurological events was less thorough than that for FS events.

Since PFO occurs in ~27% of the population, the risk of right-to-left shunt should be reduced: elevate leg during FS, have patient remain supine for at least 5 minutes after FS, and avoid Valsalva maneuver (putting on socks/shoes) and constipation (good hydration).

### *Résumé*

***Introduction :*** *L'injection d'air est inhérente à la pratique de la sclérothérapie à la mousse. Une corrélation entre la présence d'un foramen ovale persistant (PFO) et des complications neurologiques dues à des embolies gazeuses existe. Elle doit nous conduire à mieux comprendre quel est ce risque et quelle est la façon de le traiter lorsqu'il survient.*

***Méthodes :*** *Une analyse des rapports publiés sur les événements et les troubles neurologiques après sclérothérapie liquide (LS) ou sclérothérapie à la mousse (FS) a été menée à la suite d'une recherche à partir des bases de données de la littérature médicale à partir de PubMed, Embase Ovide, Medline, Medscape, et Google Scholar.*

***Résultats :*** *Onze cas de suspicion d'embolies gazeuses consécutives à la FS ont été publiés entre 2006 et 2011.*
*Trois cas ont été considérés comme des accidents ischémiques transitoires et les 8 autres cas ont été diagnostiqués comme des AVC.*
*Ces cas ont été généralement associés à des embolies artérielles paradoxales de l'artère cérébrale moyenne ou de l'artère ventriculaire et un PFO a été identifié 8 cas sur 11. Six cas suspects d'embolie gazeuse consécutifs à une SL ont été publiés entre 1947 et 2006. Un AVC a été diagnostiqué dans 4 cas et un accident ischémique transitoire dans les 2 cas restants. Alors que le PFO n'a été identifié que dans seulement 2 des 6 cas.*
*La communication des données neurologiques liés à la LS a été moins poussée que celle pour les événements secondaires à la FS.*
*On sait qu'un PFO se produit dans environ 27 % de la population. Le risque de droite à gauche shunt doit être réduit de manière préventive : il faut élever la jambe lors de la FS, le patient doit demeurer couché pendant au moins 5 minutes après l'injection de mousse, et il faut éviter de favoriser un valsalva (mise des chaussettes /chaussures, la constipation, et favoriser une bonne hydratation.*


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Foam should contain the smallest bubbles possible and be used < 90 seconds after generation. Precardial Doppler and transcranial Doppler ultrasound are the most sensitive, noninvasive monitoring methods for possible air embolisms if used skillfully.

Hyperbaric therapy may help treat cerebral arterial gas embolism if initiated < 6 hours.

**Conclusions:** Air embolisms, while rare and seldom dangerous, are an inherent risk of FS. Therefore, practitioners should be skilled in minimizing the risk, assessing neurological events, and detecting signs of air embolism effects.

***Keywords:*** *air embolism, slerotherapy, right-to-left shunt (RLS), patient foramen ovale (PFO), neurological complications.*

*La mousse doit contenir les bulles plus petites possibles et être utilisée moins de 90 secondes après sa génération. Un écho-Doppler cardiaque et transcrânien sont les plus méthodes les plus sensibles, pour la surveillance non invasive de la survenue des embolies gazeuses possibles si ces explorations sont habilement utilisées. Le traitement hyperbare peut aider à traiter l'embolie gazeuse s'il est amorcé avant la 6e heure après la survenue de l'AVC.*

***Conclusions :*** *Les embolies gazeuses bien que rares et rarement dangereuses, constituent un risque inhérent de la sclérothérapie à la mousse. Par conséquent, les praticiens doivent avoir des compétences pour en minimiser le risque, pour évaluer les événements neurologiques et détecter des signes des effets d'une embolie gazeuse.*

**Mots-clés :** embolie gazeuse, sclérothérapie à la mousse (FS), shunt droit gauche (RLS), foramen ovale permanent (FOP).

## Introduction

Sclerotherapy is a minimally invasive procedure that has been used to safely and effectively treat varicose disorders [1, 2] for decades.

Liquid sclerosants have been used for 7 decades, while foamed sclerosants have been popularized within the last 2 decades.

The incidence of complications following sclerotherapy is low, especially those potentially involving air emboli [3, 4, 5, 6, 7].

Overall, neurological complications following sclerotherapy occur in up to 2% of patients [5].

Yet, in a review of 10,819 patients who had liquid or foam sclerotherapy.

Sarvananthan et al. reported the frequency of neurological compilations following sclerotherapy as approximately 0.9% [6].

In a study of 1,025 patients treated with foam sclerotherapy (FS), Gillet et al. reported one case of transient ischemic attack (TIA, 0.1%) and a 2% prevalence rate of migraine or visual disturbance [4].

Similarly, in a literature review of 104 reports, Jia et al. assessed over 9,000 patients treated with FS and revealed one case of stroke [3]. They also revealed 141 cases of visual disturbances (1.4%) and migraine (4.2%); 15 of these cases were found to have a patent foramen ovale (PFO), but not all cases were evaluated for PFO [3].

Iatrogenic air embolisms with neurological complications after sclerotherapy, although rare, have been reported and have come under increasing scrutiny.

An association between neurological events and disturbances after sclerotherapy with the presence of a PFO has been reported.

Fortunately, cases are rare and most patients had no residual deficits [3, 4, 6].

However, since the prevalence of PFO is approximately 27% in the general population [8] and injection of air is an inherent part of FS, a correlation, if present, would be important in understanding the risks of air embolisms and how to treat them when they occur in conjunction with sclerotherapy.

Therefore, an analysis of published cases was performed to further assess potential risks of air embolism associated with sclerotherapy and for identifying preventative methods.

Published reports of neurological events and disturbances after liquid sclerotherapy (LS) or FS were identified and assessed for this analysis.

## Methods

A literature review was conducted by searching several electronic databases: PubMed, Ovide Embase, Medline, Medscape, and Google Scholar.

Keywords and phrases used to search these databases included combinations of air embolism, sclerotherapy, foam sclerotherapy, neurological, stroke, and complications.

Peer-reviewed journal articles, conference abstracts, and journal letters were limited to those published in English or French.

Neurological events or disturbances had to occur during or shortly after sclerotherapy and result from suspected air embolisms.

| Case | 1st Author, Year | Age/Sex | Varicose vein | Rx | Concentration (%) | Volume (mL) | Event | Time to Event/ Recovery | Patent foramen ovale | Sequelae |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Forlee, 2006 [9] | 61/M | Great saphenous vein | Polidocanol | 0.5 | 20 | Stroke | – | × | Yes |
| 2 | Bush, 2008 [10] | 72/F | Great saphenous vein | Sodium tetradecyl sulfate | 2 | 2 | Transient ischemic accident | 25 minutes/ 3 hours | × | No |
| 3 | Bush, 2008 [10] | 35/F | Reticular veins | Sodium tetradecyl sulfate | – | 10 | Stroke | 5 minutes | Atrial septal defect | Yes |
| 4 | Leslie-Mazwi, 2009 [11] | 38/F | – | Sodium tetradecyl sulfate | – | – | Stroke | 10 minutes/ 2 hours | Middle cerebral artery * | Yes (T) |
| 5 | Hartmann, 2009 [12] | 37M | Great saphenous vein | Polidocanol | 3 | 9 | Transient ischemic accident | 2 hours | × | No |
| 6 | Picard, 2010 [13] | 33/M | Great saphenous vein | Polidocanol | 0.5 | 4 | Stroke | 4 hours | × | No |
| 7 | Hahn, 2010 [14] | 48/F | Small saphenous vein | Polidocanol | 1 | 3 | Stroke | 5 days | × | No |
| 8 | DeLaney, 2010 [15] | 38/F | – | Sodium tetradecyl sulfate | 0.5 | 2 | Transient ischemic accident | 20 minutes/ < 24 hours | Middle cerebral artery * | No |
| 9 | Ma, 2011 [16] | F | Great saphenous vein | Sodium tetradecyl sulfate | 3 | 16 | Stroke | 2 days | × | No |
| 10 | Ma, 2011 [16] | F | Great saphenous vein | Sodium tetradecyl sulfate | 1.5 | 4 | Stroke | 5 minutes | × | No |
| 11 | Ma, 2011 [16] | F | Great saphenous vein | Sodium tetradecyl sulfate | 3 | 25 | Stroke | 1 day | × | No |

***TABLE 1 : Neurological Events After Foam Sclerotherapy.***
* Air in MCA but PFO not mentioned.

Eleven articles reporting 17 cases of neurological complications associated with air embolism were identified: 8 articles that reported 11 cases following FS and 6 articles that reported 6 cases following LS.

# Results

## Cases Following Foam Sclerotherapy

Eleven cases of suspected air embolism following FS were published between 2006 and 2011 and are summarized in Table 1.

The cases comprised 8 females (61.5%) and 3 males (38.5%).

The mean age for 8 of these patients was 45 years (33 to 72 years); age was not provided for 3 patients.

The majority of these patients (72.7%) were undergoing treatment of large veins (i.e., great saphenous vein [GSV], small saphenous vein [SSV], perforator veins), while 9.1% were being treated for small veins (i.e., reticular veins, telangiectases).

Two sclerosants were primarily used in these cases: 0.5% to 3% POL or STS. The volume of sclerosant used in these cases ranged from 3-20 mL for polidocanol (POL) and 2-25 mL for sodium tetradecyl sulfate (STS).

A majority of patients developed symptoms immediately after their first treatment; in other patients, events occurred after 2-4 sessions.

| Case | 1st Author, Year | Age/Sex | Varicose vein | Rx | Concentration (%) | Volume (mL) | Event | Time to Event/ Recovery | Patent foramen ovale | Sequelae |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Gardner, 1947 [17] | 32/F | Telangiectases | Sodium morrhuate | 5 | 0.75 | TIA | 2 minutes/ 4 hours | – | No |
| 2 | Peller, 1951 [18] | 62/F | – | Sodium morrhuate | 5 | 2 | Stroke | 5 minutes/ 16 hours | – | Death |
| 3 | Drai, 1994 [19] | – | – | – | – | – | Transient ischemic accident | – | × | No |
| 4 | Van der Plas, 1994 [20] | – | Great saphenous vein | – | 2 | 2 | Stroke | – | – | – |
| 5 | Kas, 2000 [21] | – | Telangiectases | CG | – | 1 | Stroke | – | – | – |
| 6 | Hanisch, 2004 [22] | 54/F | Reticular veins/ Telangiectases | Polidocanol | 0.5 | 0.5 | Stroke | 3 days | × | – |

*TABLE 2 : Neurological Events Following Liquid Sclerotherapy.*

While most events occurred within 5-20 minutes after treatment, in some cases the occurrence of cerebral air embolism was not recognized until an explanation was sought for the sudden development of a neurological deficit.

Three cases were diagnosed as transient ischemic attacks (TIA), and the remaining 8 cases were diagnosed as strokes.

These cases were typically associated with paradoxical arterial embolisms of the middle cerebral artery (MCA) or ventricular artery (VA) by the authors [10, 11, 13, 15].

### Cases Following Liquid Sclerotherapy

The 6 cases of suspected air embolism following LS were published between 1947 and 2006 and are summarized in Table 2.

The data reported for the LS neurological events was less thorough than that reported for FS events.

Three cases involved female patients with a mean age of 49.3 years (32-62 years); the patients' sex and age were not available for 3 cases.

Three patients were undergoing treatment for small veins (i.e., reticular veins, telangiectases) and one for large veins (i.e., GSV); the veins being treated were not identified for 2 cases.

In addition, the sclerosant was not identified in 2 cases and 2 cases involved sodium morrhuate, which is currently used infrequently compared to POL and STS.

Stroke was diagnosed in 4 cases and TIA was diagnosed in the remaining 2 cases.

## Discussion

While cases following FS were diagnosed as TIA or strokes, the mechanism behind the complications is poorly explained in some of the articles assessed.

Thus, it is unclear if air bubbles, the sclerosant, or debris resulting from the procedure were associated with the neurological complications.

Air has been observed in MCA by several researchers without symptoms in most of studied patients [23, 24].

### Patent Foramen Ovale

It is known that an introduction of air into the venous circulation can cause cerebral air embolism.

The presence of a PFO can allow a right-to-left shunt (RLS) for venous air to embolize to the cerebral arteries. The prevalence of PFO is approximately 27% of the general population [8] and 34% in younger persons [25] and most are undiagnosed.

Therefore, physicians performing sclerotherapy must be aware of the signs and symptoms that can signal an air embolism. Sarvanathan et al. have demonstrated through an extensive case review that neurological complications that occur within minutes of sclerotherapy are most likely related to an air embolism rather than a paradoxical clot embolism [6].

During or following sclerotherapy, an air embolism should be considered if any of the following symptoms are noted: acute dyspnea, continuous cough, 'gasp' reflex, dizziness, light headedness, vertigo, nausea, substernal chest pain, agitation, disorientation, or a sense of impending doom [26, 27].

Additional neurological, opthalmological, and cutaneous signs and symptoms include transient/permanent focal deficits (weakness, paresthesias, paralysis of extremities), loss of consciousness (collapse), coma (secondary to cerebral edema), acutely altered mental status, seizures, crepitus over superficial vessels (rarely seen in setting of massive air embolus), livedo reticularis, and air bubbles in the retinal vessels revealed by funduscopic examination [28].

While the presence of a PFO is a risk factor for air embolism, its presence does not necessarily guarantee that an air embolism will occur.

It is not always clear why some patients experience neurological events and disturbances and others do not. The full spectrum of risk factors must be contemplated when assessing complications associated with sclerotherapy.

While PFO size seems to be a negligible variable [29], for an air embolus to reach the brain from a peripheral vein, a number of conditions may be relevant: the orientation of the caval ostium in the right atrium, the persistence of an Eustachian valve, the relative eccentricity of ostium primum and ostium secundum, and the anatomy of supra-aortic vessels.

All these factors may contribute to modify the amount of blood that passes through a RSL and potentially to the brain.

In any case, the greater the shunt to the brain, the greater the likelihood that an air embolus can threaten the brain vessels [30].

While screening all patients for PFO before sclerotherapy is not warranted, screening may be warranted in patients with severe co-morbidities or a history of cryptogenic embolic stroke, migraine with an aura, platypnea orthodeoxia, transient amnesia, TIA, retinal thrombosis, stroke with chronic obstructive pulmonary disease, pulmonary hypertension, or sleep apnea, as these conditions have been associated with PFO.

## Other Risk Factors for Air Embolisms and Neurological Events

In addition to PFO, other factors implicated in the event of air embolisms after FS treatments include technique, volume of sclerosant used, speed of injection, the generation of microbubbles as compared to macrobubbles, air as compared to $CO_2$ or other gases, patient position, and Valsalva-like maneuvers.

The most important measure in reducing the risk of any event following sclerotherapy is to obtain adequate training and knowledge and to conduct procedures with care and attention [31].

It is commonly held that injecting large volumes foam presents a higher risk of developing neurological complications, but there have been cases reported in which < 10 mL of foam were used [6].

Therefore, the volume of foam used during sclerotherapy should be minimized. A common sclerosant-to-air ratio used in generating foam is 1:4, thus every 1 mL reduction in the volume of foam sclerosant used represents a 0.8 mL reduction in the amount of air induced into the venous system.

Traditionally, it has been estimated that > 5 mL/kg of air displaced into the intravenous space is required for significant injury.

However, complications have been reported with as little as 2 mL of foam injected intravenously [10, 15]. In addition to the amount of air or gas used, the size of the bubbles constituting the foam is significant.

The smallest bubbles possible should be used, by using the 3-way Tessari method [32], vial Raymond-Martimbeau method [33], connector method, or pump method, to increase the solution's contact with the endothelium and to reduce mixing of foam and blood after injection [34]; in addition, smaller bubbles have a greater surface area, which speeds up gas reabsorption [5].

The foam should be used quickly (within 90 seconds) and be discarded if any signs of coalescence are noted.

The number of injections can also affect the risk of paradoxical air emboli. It has been shown that using multiple injections of < 0.5 mL of foam per site in treating varicose tributary veins reduced the amount of air that entered the deep venous system [35]. Another factor can be the gas used to generate the sclerosing foam.

For example, $CO_2$ may be tolerated by patients better than air because it is 25 times more soluble in blood than nitrogen, which makes up approximately 79% of air.

$CO_2$ is eliminated quickly, as well, due to bicarbonate buffering, which helps explain why its lethal dose is approximately 5 times higher than air [36].

Air embolism may also result from the iatrogenic creation of a pressure gradient for air entry. Thus, during sclerotherapy, the risk of bubbles moving caudally can be reduced by placing patients supine with the treated leg elevated during and shortly after the procedure [37].

Additionally, avoid head elevation or sitting positions during the procedure and shortly thereafter. Valsalva-like maneuvers can potentiate a RSL if a PFO is present, thus should also be avoided.

While the use of catheters to inject sclerosant along a vein has been explored [38], it must be kept in mind that air can be introduced during catheter insertion or injection due to the increased dead space.

In addition, deep inspiration during insertion or removal of catheter or needle can increase the magnitude of negative pressure and raise the possibility of air embolism.

It should be noted that not all neurological events or disturbances are attributable to air embolism.

A few theories have been formulated to explain events not related to emboli.

Cytokines, such as endothelin 1 which is a strong vasoconstrictor, are released from the vessel lining when damaged [39].

Destruction of the endothelium during sclerotherapy may cause a immediate release of endothelin 1 that reaches the arterial circulation through a RLS, resulting in migraine with aura [6] as well as headache, visual disturbances, and other events associated with vasoconstriction.

Similarly, microbubbles in circulation can precipitate platelet aggregation and the release of platelet activator inhibitor, which may lead to systemic inflammatory response syndrome [26], which can present with increased heart and respiratory rates and lead to respiratory distress, central nervous system dysfunction, or coma.

## Methods for Detecting Air Embolism

There are numerous methods of detecting intravenous air when air embolism is suspected.

However, most laboratory tests are neither sensitive nor specific. In addition, many tests require equipment that is not appropriate for a medical office.

Transesophageal echocardiography is invasive, may require sedation of the patient, is costly, and entails specialized training in conducting and interpreting the test.

For precordial Doppler ultrasound to be sensitive in detecting air emboli, the placement of the Doppler probe is crucial [40], thus, without extensive training, the sensitivity of the test is compromised.

Chest X-rays and computerized tomography (CT) scans can show gas in the pulmonary arterial system or cerebral air, respectively; however, the equipment and training necessary to conduct these tests are prohibitive for a medical office.

Bilateral contrast transcranial Doppler (cTCD) can be used to determine the absence or presence of PFO in an office setting, as the device is small and the procedure is uncomplicated.

To conduct a cTCD ultrasound, a small probe was placed on the temple just above the ear directing ultrasound waves in order to locate the flow of blood in the middle cerebral artery.

Agitated saline solution (i.e., 1 mL air to 9 mL saline) is injected intravenously and a Valsalva maneuver is used as the provocation procedure.

If a RLS exists, microbubbles pass unfiltered by the lungs through the shunt, and travel to the arteries of the cerebral circulation.

Ultrasound waves strongly reflect the microbubbles and are detected by the probe as high intensity transient signals (HITS).

The Spencer Grading System, a 1-5 rating system, is used to categorize the number of HITS recorded. A higher grade, that is more HITS, reflects a larger amount of blood being shunted, which indirectly represents a larger PFO [7].

Transcanial duplex ultrasound can be used to detect air embolisms in the cerebral arteries. The main advantage of this method is that the equipment is commonly found in the medical office, thus it is immediately available, requires limited additional training, and is cost effective. **Images showing the presence of air in the cerebral artery are provided in Figure 1.**

Other tests that can possibly indicate the presence of an air embolism are electrocardiogram, end-tidal carbon dioxide, and end-tidal nitrogen. However, these tests are not sensitive or specific for venous air embolism, thus may provide false positive or negative results.

## Management of an Air Embolism

If an air embolism is suspected, immediate appropriate management of the event is crucial.

At the first signs or symptoms of a potential embolism, discontinue the sclerotherapy, place the patient in a left lateral decubitus position (i.e., Durant maneuver) [41], and administer 100% oxygen.

If circulatory collapse occurs, move the patient into a supine position with legs elevated and initiate CPR. If signs and symptoms persist, the patient should be evacuated to emergency facilities for hyperbaric treatment.

Air transportation should be avoided, as altitude reduces barometric pressure and can allow the air embolism to expand and exacerbate the patient's condition.

The literature supporting the administration of hemodynamic medications, such as dobutamine and norepinephrine, is limited primarily to research in dogs [26].

## Prevention of Air Embolisms during Foam Sclerotherapy

The prevention of air embolisms begins before the patient arrives at the clinic.

Patients should be instructed to adequately hydrate before the procedure since dehydration can decrease venous pressure making it easier for bubbles to circulate.

In addition, patients may be advised to use a stool softener before and after FS to avoid constipation and associated Valsalva maneuvers after the procedure.

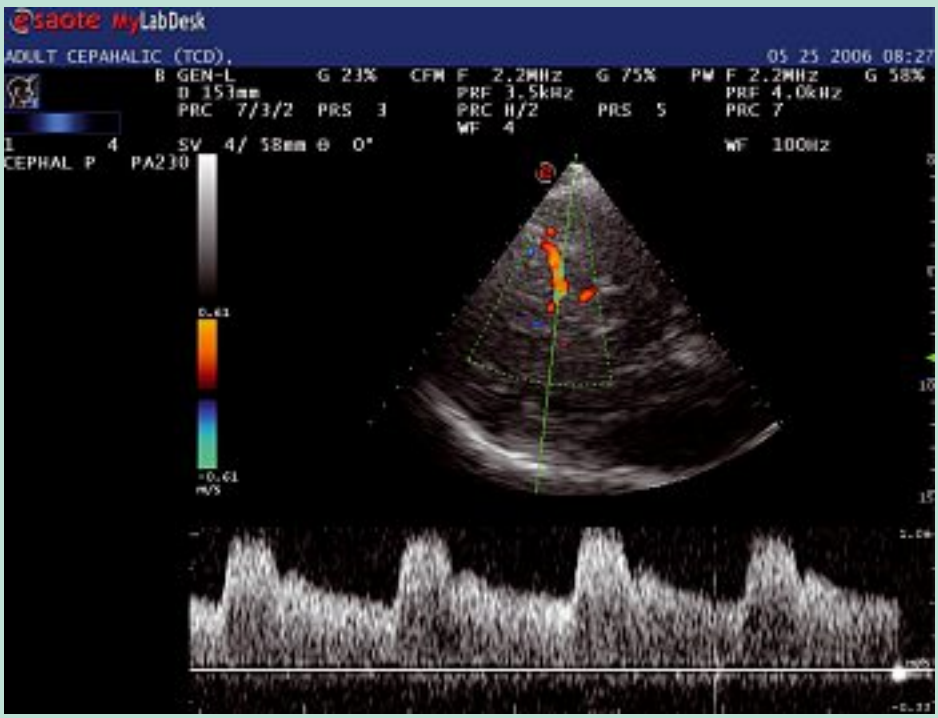


*FIGURE 1 : Transcranial duplex ultrasound showing air embolism in the middle cerebral artery following saline test.*

## Conclusions

Air embolisms, while rare and seldom dangerous, are an inherent risk of FS. Therefore, practitioners should be skilled in minimizing the risk, assessing neurological events, and detecting signs of air embolism effects.

To enhance our understanding of air embolisms associated with FS, it is essential that practitioners report all cases in journal articles or letter.

The creation of a national or international registry would also augment research in this area and support continuous improvements in FS procedures.

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