Hyperbaric Oxygen Therapy for Cerebral Arterial Air Embolism Secondary to Transbronchial Lung Biopsies: More Air than Substance?

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ABSTRACT Cerebral arterial air embolism (CAAE) is a rare, but often fatal, complication of interventional bronchoscopy. Despite its rarity, a high index of suspicion can facilitate early diagnosis and prompt treatment. Standard of care treatment for CAAE is hyperbaric oxygen therapy, despite limited definitive data supporting its efficacy, given the conceptual potential for reversibility of neurological impairment. We describe five cases from our institution, and review the clinical presentation, pathophysiology, diagnosis, and management of suspected CAAE. Based on published case reports involving transbronchial lung biopsies (TBLB), standard of care treatment for CAAE secondary to TBLB is hyperbaric oxygen therapy, although its efficacy in this context has not been unambiguously validated in clinical practice.

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KEY WORDS: bronchoscopy, cerebral arterial air embolism (CAAE), hyperbaric oxygen therapy, transbronchial lung biopsy (TBLB)

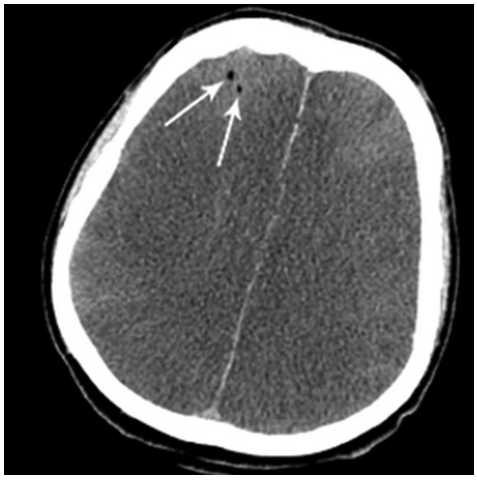
Cerebral arterial air embolism (CAAE) is a rare complication of interventional procedures that involve or impact the vasculature, such as cardiovascular and neurological endovascular procedures [1]. Interventional bronchoscopy for the diagnosis and management of lung pathologies is a relatively safe procedure with low associated morbidity and mortality [2]. In the setting of interventional bronchoscopy, the incidence of CAAE is less well-established, reported primarily in bronchoscopy involving argon plasma coagulation (APC) [3] and laser treatments [4]. We present five cases of suspected CAAE from our institution to illustrate the risks and diagnostic challenges of CAAE secondary to interventional bronchoscopy. Given the potentially catastrophic consequences of CAAE, practitioners must be aware of both early signs of CAAE and treatment options to mitigate the effects of CAAE when suspected.

CEREBRAL ARTERIAL AIR EMBOLISM IS A RARE BUT OFTEN FATAL COMPLICATION OF TRANSBRONCHIAL LUNG BIOPSIES.

CASE 1

An 82-year-old male with pulmonary amyloidosis presented with persistent non-productive cough. A chest computed tomography (CT) demonstrated multiple parenchymal pulmonary masses and stenosis of the left main bronchus, compatible with extensive pulmonary amyloidosis. Neodymium yttrium-aluminum garnet (Nd:YAG) bronchoscopic laser photocoagulation was performed to ablate the obstructing mass. During the procedure, the patient developed severe hypotension and bradycardia, deteriorating to asystole. Cardiopulmonary resuscitation restored spontaneous circulation; however, neurologic examination revealed reduced consciousness, constricted pupils, increased muscle tone, and positive bilateral Babinski reflexes. Head CT demonstrated signs of severe anoxic brain damage, tonsillar brain herniation, and air vesicles in the frontal lobe consistent with air emboli [Figure 1]. The patient was transferred to an intensive care unit, placed on respiratory and hemodynamic support; however, hyperbaric oxygen therapy was not pursued considering his poor prognosis. The patient died the following day.

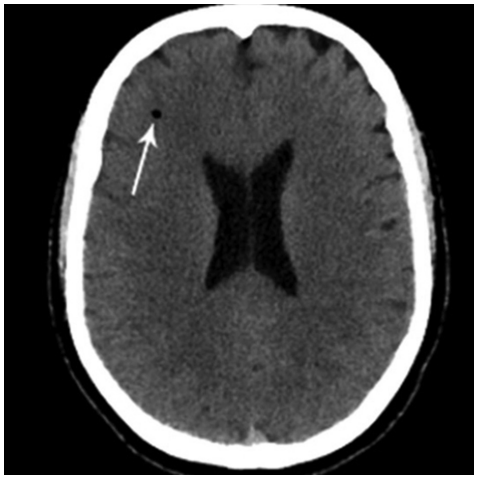
Figure1. Head computed tomography, axial plane, centrum semi ovale level; shows air emboli in the right frontal lobe



CASE 2

A 55-year-old female with chronic obstructive pulmonary disease was referred for bronchoscopy due to atelectasis of the right lower lobe. Flexible bronchoscopy revealed significant stenosis in the intermediate right bronchus. The lumen was dilated with Nd:YAG bronchoscopic laser photocoagulation followed by dilation with an intra-bronchial balloon. On discontinuation of sedation, the patient remained unconscious. A head CT demonstrated multiple small air vesicles in the right cerebral hemisphere [Figure 2]. Following intubation, the patient was urgently transferred to a tertiary hospital for hyperbaric oxygen therapy but was pronounced dead on arrival.

Figure 2. Head computed tomography, axial plane, lateral ventricles level; shows air emboli in the right frontal lobe



CASE 3

A 73-year-old female with hypothyroidism underwent bronchoscopy using a navigational guidance system to biopsy with a cryo-probe a 2-centimeter opacity in the left lower lobe incidentally discovered after a syncopal event. The procedure was uneventful; however, in the recovery room after the procedure, the patient was unable to be awoken. An initial head CT demonstrated no acute findings, whereas a chest CT demonstrated a left hydro-pneumothorax and pneumo-mediastinum, and a chest tube was placed with partial resolution. Subsequently, the patient was observed to experience seizure activity and anti-epileptic treatment was commenced. Due to lack of clinical neurological improvement, the patient was sedated, intubated, and transferred for hyperbaric oxygen therapy within 12 hours of the bronchoscopy procedure. After treatment, she returned to the intensive care ward, was extubated and continued on anti-epileptic treatment. She was subsequently transferred to the general medical ward and then discharged to a rehabilitation center where she partially improved neurologically. A subsequent brain magnetic resonance imaging (MRI) 5 days after the event demonstrated cerebral cortical and subcortical acute micro-infarcts, suggestive of ischemic damage secondary to air emboli, but not definitively dispositive.

CASE 4

A 55-year-old female with endobronchial sarcoidosis, status post-endobronchial stents in the right middle lobe and left lower lobe bronchi, presented for routine bronchoscopic follow-up. The patient underwent balloon dilation for both stents. After the procedure, the patient was irritable with left hemiparesis and right eye deviation. An initial head CT demonstrated no acute findings. The patient subsequently became febrile, attributed to aspiration secondary to the patient's decreased state of consciousness. An electroencephalogram showed no signs of epileptic activity. After lack of improvement, the patient was sedated, intubated, and transferred for hyperbaric oxygen therapy. After treatment, the patient was extubated and returned to the intensive care unit where she received antibiotics for aspiration pneumonia. She was then transferred to the general medical ward where she gradually regained full strength and movement of her left arm and leg. She subsequently discharged without signs of neurological deficits.

CASE 5

A 69-year-old female with metastatic melanoma and breast cancer underwent bronchoscopy to biopsy a lung

mass in the right upper lobe and proximal lymph nodes. During the procedure, there was localized bleeding, which resolved after treatment with intravenous tranexamic acid and cooled normal saline irrigation. Approximately an hour after the procedure in the recovery room, the patient was difficult to awaken and showed signs of aphasia and left sided weakness. An initial CT scan of the head did not demonstrate any acute findings. Her cognitive condition deteriorated, with response only to painful stimuli. A brain MRI was performed with no findings that could explain her condition. Subsequently, the patient was observed to experience seizure activity and anti-epileptic treatment was commenced. She was sedated, intubated, and transferred to a tertiary hospital for hyperbaric oxygen therapy. After treatment, the patient did not demonstrate neurological improvement. She was returned to the intensive care unit where attempts to extubate her were unsuccessful. A subsequent MRI one week later demonstrated frontal lobe gyral enhancement consistent with status epilepticus, and she was discharged after tracheostomy to a center for respiratory rehabilitation.

A HIGH INDEX OF SUSPICION CAN FACILITATE EARLY DIAGNOSIS AND PROMPT TREATMENT IN THE PRESENCE OF SUGGESTIVE NEUROLOGICAL AND CARDIOVASCULAR SIGNS AND SYMPTOMS.

DISCUSSION

CAAE is a well described, although rare, risk of invasive procedures, principally reported during endovascular procedures [1]. Although often a self-limited condition, it carries the potential for significant morbidity, including stroke and death [1]. The overall incidence of CAAE during bronchoscopy is difficult to assess due to its rarity. One study estimated the frequency at less than 1 event per 100,000 procedures [2]. In the context of interventional bronchoscopy, various reviews have reported CAAE in bronchoscopy procedures involving laser or gas treatments [3,4]. The incidence of CAAE in bronchoscopy procedures involving transbronchial lung biopsy (TBLB) and transbronchial needle aspiration (TBNA) is less well-studied and is limited to case reports. Table 1 details 23 case reports describing CAAE in the context of TBLB/TBNA, of which 20 demonstrated diagnostic imaging evidence of CAAE. Incidence of CAAE in the context of TBLB/TBNA based on our limited single-center experience is less than 1 event per 2000 TBLB/TBNA procedures.

SIGNS AND SYMPTOMS

CAAE can result in a spectrum of neurological signs and symptoms, ranging from headache, confusion and localized motor weakness to extensive paresis, convulsions, impaired consciousness, and death [5]. In the setting of post-bronchoscopy recovery, impaired consciousness, delayed recovery from sedation, seizures, or focal neurological deficits may be suggestive of CAAE [6]. Practitioners should have a heightened clinical suspicion for CAAE when there is a clear temporal relationship between an invasive procedure and subsequent cardio-pulmonary instability or neurologic symptoms [7]. Unfortunately, these features are non-specific and can be attributed to other etiologies. Patients experiencing CAAE are more likely to have concurrent medical problems such as cerebrovascular disease, cardiovascular disease, and metabolic disorders [7]. These factors, as well as pharmacological sedation, can all produce neurological impairment and therefore expand the differential diagnosis. Given that symptoms are variable and overlap with other conditions, practitioners should maintain a broad differential diagnosis for post-bronchoscopy impaired responsiveness, including ischemic stroke, cardiac events, hemorrhage, drug reactions, hypoglycemia, and metabolic derangements [7]. While CAAE must be considered when a patient is unresponsive, given its potential reversibility with prompt treatment, it is important to consider all potential causes and pursue appropriate diagnostics and treatments consistent with the presentation and findings.

PATHOPHYSIOLOGY

The venous circulation is at an increased risk for air emboli due to its relatively low-pressure system [1]. Vascular air emboli that enter from the right heart through the pulmonary arteries are generally eliminated in the lungs by diffusion through the alveolar membrane [7]. Air emboli are less likely to directly enter the higher pressure arterial circulation; rather, they are generally found in the systemic circulation secondary to a physiologic shunt, such as a septal defect, patent foramen ovale, or pulmonary arteriovenous malformation [1]. However, emboli can also pass through the pulmonary circulation and enter the left heart even in the absence of a shunt if the pressure and flow overwhelms the pulmonary filtration capacity [7]. Specifically, increased air volume and rate of entry into circulation may overwhelm the diffusion capacity of the lung and, as such, both volume and rate can influence the likelihood of CAAE [7].

Air emboli not eliminated in the lungs travel through the pulmonary veins to the left heart, from where they

Table 1. Summary of case reports of cerebral arterial air embolism during bronchoscopy involving TBLB or TBNA

Case No.	Author, year, reference number	Sex/Age	Underlying disease	Suspected disease	Procedure	Examined lung lobe	Clinical presentation	Air emboli on CT	Treatment	Site of embolization	Outcome
1	Erickson et al. 1979 [14]	Male/48	Alcoholic liver disease	Tuberculosis	TBLB	RLL	Tachycardia, comatose, B/l Babinski reflex	(+)	N/A	Retinal arterial air emboli	Death
2	Shetty et al. 2001 [15]	Male/60	N/A	IPF	TBLB	N/A	Hypotension, bradycardia, convulsions	(+)	HBO_2	Bilateral CAAE	Death
3	Wherrett et al. 2002 [5]	Male/70	COPD, HTN, Smoker	Lung cancer	Oxygen insufflation	RUL	Unresponsive, desaturation, convulsions	(-)	HBO_2, 52 hours after event	Not confirmed by imaging	Recovered
4	Dhillon et al. 2004 [16]	Male/55	COPD	Lung cancer	TBLB, TBNA	RLL	Left facial weakness, left hemiplegia	(+)	NBO_2	Right frontal lobe CAAE	Recovered
5	Maricich et al. 2004 [17]	Male/55	Rectal carcinoma	Lung mass	TBLB	N/A	Seizure, disorientation, left hemiparesis	(+)	N/A	Bilateral CAAE	Recovered
6	Azzola et al. 2010 [18]	Female/60	N/A	Lung cancer	TBNA, TBLB	LUL	GCS 7/15	(+)	HBO_2	Bilateral CAAE	Death
7	Azzola et al. 2010 [18]	Female/68	COPD, CAD	Lung cancer	TBNA, brush cytolo.	RLL	Anisocoria, GCS 4/15	(+)	N/A	Left hemisphere CAAE	Death
8	Delannoy et al. 2010 [19]	Male/58	Laryngeal cancer	Endobronchial lesion	TBLB	RUL	General seizure, comatose, GCS 3/15	(+)	HBO_2	Bilateral CAAE	No recovery
9	Perinel Ragey et al. 2013 [20]	Male/70	COPD	Lung cancer	TBNA, brush cytolo.	LUL	Convulsions, left hemiplegia	(+)	HBO_2	Right hemisphere CAAE	Recovered
10	Evison et al. 2014 [21]	Female/84	N/A	Lung cancer	TBLB	RUL	GCS 3/15, convulsions	(+)	NBO_2	Bilateral CAAE	Partially recovered
11	Goto et al. 2014 [22]	Male/69	Hypopharyngeal cancer	Lung cancer	TBNA, TBLB	LUL	Decreased consciousness, hemiplegia	(+)	HBO_2	Right occipital lobe and parietal lobe CAAE	No recovery
12	Dong et al. 2014 [23]	Male/63	IPF s/p lung transplant	Anastomotic stenosis	TBLB	LMB	Altered, dysarthric,ataxic	(+)	N/A	Right cerebellar tonsil infarcts, left retinal emboli	Recovered
13	Tsuji et al. 2017 [24]	Male/51	COPD	Tuberculosis	Curettage, TBLB	RUL	Bradycardia, left hemiplegia	(+)	N/A	Left occipital CAAE	Recovered
14	Maemura et al. 2018 [9]	Male/77	COPD	Lung cancer	Curettage	RLL	Left hemiplegia, L spatial neglect, convulsions	(+)	NBO_2	Right hemisphere CAAE	Partially recovered
15	Fogelfeld et al. 2018 [25]	Male/61	Asthma, hypertension, diabetes	Lung nodule	TBLB, lavage	LLL	Left gaze preference, seizure	(+)	HBO_2	Right hemisphere CAAE	Recovered
16	Almas et al. 2018 [6]	Male/69	Emphysema	Lung cancer	TBNA	Right Hilum	Unresponsive, left side hemiparesis	(-)	N/A	Not confirmed by imaging	Recovered
17	Almas et al. 2018 [6]	Male/69	N/A	Lung cancer	TBNA	Right Hilum	Unresponsive, left side hemiparesis	(+)	N/A	Right hemisphere - MCA territory CAAE	Recovered
18	Rebelo et al. 2018 [26]	Female/17	Hodgkin Lymphoma	Lung mass	TBLB	LUL	Unresponsive, decerebrate movements	(+)	HBO_2	Cortical air emboli and infarctions	Death
19	Toyota et al. 2019 [27]	Female/88	N/A	Lung cancer	TBLB	RLL	Right conjugate, deviation, left hemiplegia	(+)	HBO_2	Left occipital CAAE	Recovered
20	Van Den Plas et al. [28] 2020	Male/78	Former smoker	Fibrotic lung disease	TBNA	Carina (lymph node 7)	Unresponsive, bilateral Babinski sign	(+)	NBO_2	Left occipital CAAE	Partially recovered
21	Herout et al. 2021 [29]	Male/70	N/A	Lung cancer	TBLB	RLL	Right mydriasis, right facial cyanosis	(+)	HBO_2	Air in venous system of right hemisphere	Death
22	Swenson et al. 2021 [13]	Male/48	Former smoker	Lung nodule	TBLB	Lingula	AV block, left facial droop, left monoplagia	(-)	NBO_2	Not confirmed by imaging	Recovered
23	Bilali et al. 2022 [30]	Male/85	Hypertensin, Diabetes	COVID-19	TBLB	N/A	Drowsiness, convulsions	(+)	NBO_2	Diffuse frontal, parietal emboli	Death
24	Heching et al.	Female/73	Hypothyroidism	Lung nodule	TBLB	LLL	Unresponsive, seizures	(-)	HBO_2	Not confirmed by imaging	Partially recovered
25	Heching et al.	Female/69	Metastatic melanoma, breast cancer	Lung mass	TBLB, EBUS	RUL	Aphasia, left sided weakness	(-)	HBO_2	Not confirmed by imaging	No meaningful recovery

TBLB = transbronchial lung biopsy, TBNA = transbronchial needle aspiration, HBO_2 = hyperbaric oxygen, NBO_2 = normobaric oxygen, COPD = chronic obstructive pulmonary disorder, CAD = coronary artery disease, APC = argon plasma coagulation, GCS = Glasgow Coma Scale, RUL = right upper lobe, RLL = right lower lobe, RML = right middle lobe, LUL = left upper lobe, LLL = left lower lobe, MI = myocardial infarction, IPF = idiopathic pulmonary fibrosis, EBUS = endobronchial ultrasound

can pass through the systemic circulation to any organ [7]. The air can obstruct capillaries, leading to local inflammatory response and distal reduction in perfusion and ischemia [10]. The coronary and cranial arteries represent the greatest risk for critical occlusion, as the heart and brain are highly oxygen dependent [11]. Coronary air emboli can result in myocardial ischemia, arrhythmias, heart failure, and even cardiac arrest [12]. The skeletal muscles and other organs can endure relative hypoxia secondary to air emboli; however, occlusion of coronary or cerebral arteries may be life threatening due to the vulnerability of the heart and brain to even short periods of hypoxia [13].

CAAE can occur when air is entrapped in the pulmonary venous capillaries and circulates through the left heart through the systemic circulation to the brain [1]. The air emboli can lodge in narrow arterioles, particularly in the heart and brain, leading to arrhythmia, cardiac failure, hypotension, ischemia, and neurological damage [7]. The embolic damage is attributable to both lack of perfusion distal to the emboli and to a peri-embolic inflammatory response [3]. The pathophysiological mechanism causing CAAE during bronchoscopy is thought to arise from highly pressurized air being brought close to a compromised vessel [8]. The resulting high-pressure gradient enables air to enter through a broncho-vascular fistula into the relatively lower pressure vasculature [9]. Such fistulas may form secondary to thermal damage caused by invasive bronchoscopy procedures involving Nd:YAG laser ablation and APC [3,4]. In the setting of such treatments, gas flow, introduced to cool the tip of the laser probe, contributes more air to the damaged tissue site and exacerbates the high-pressure gradient that favors air entry into the vasculature [8].

The mechanism causing CAAE in the context of transbronchial biopsy is less well understood. Various hypotheses have been suggested, generally involving a combination of high airway pressures, communication between the airways and the pulmonary venous circulation, and patient-specific characteristics lengthening the patency of the communication (e.g., fibrosis, cancer, cough) [8]. In particular, the use of a transbronchial needle or forceps during biopsies may form a temporary port between the bronchus or alveola and an adjacent pulmonary vessel and create a communicating fistula for air to pass into the vessel [9]. Furthermore, occlusion of the bronchial tree by the bronchoscope can elevate distal pressure. Actions that mimic Valsalva maneuvers, such as coughing or deep inhalation during the procedure, as well as positive pressure ventilation, can further increase pressure distal to the bronchoscope [9]. The resulting high pressure gradient may enable air to enter through a broncho-vascular fistula into the relatively lower pressure vasculature.

STANDARD OF CARE TREATMENT FOR CEREBRAL ARTERIAL AIR EMBOLISM, SECONDARY TO TRANSBRONCHIAL LUNG BIOPSY, IS HYPERBARIC OXYGEN THERAPY, DESPITE LIMITED DEFINITIVE DATA SUPPORTING ITS EFFICACY, BECAUSE OF THE CONCEPTUAL POTENTIAL FOR REVERSIBILITY OF NEUROLOGICAL IMPAIRMENT.

DIAGNOSIS

Diagnostic imaging can provide a definitive diagnosis when air bubbles are identified in the vasculature or viscera [7]. However, air emboli are often absorbed or eliminated in the interim period between symptom onset and imaging, leading to the potential for false negative results on imaging [13]. Moreover, imaging findings can be subtle and overlooked given the rarity of air emboli in this setting [13]. In the presence of suggestive neurological symptoms, a head CT should be promptly attained. Where available, alternative diagnostic modalities to elucidate the presence of air emboli include MRI (greater sensitivity than CT), bedside echocardiography, and ophthalmic retinal evaluation [8]. In the published case reports, three cases did not demonstrate air emboli on imaging, raising the potential for an alternative etiology for the symptoms. Nevertheless, lack of definitive evidence on imaging should not delay treatment when CAAE is clinically suspected.

MANAGEMENT

When CAAE is suspected, in addition to airway management and hemodynamic support, practitioners should consider corrective actions to prevent further entry of air into the vasculature, and to mitigate the effects of existing air emboli. A plain chest film is required to check for pneumothorax, and a chest tube is placed if present. Left lateral decubitus and Trendelenburg positioning is recommended when venous embolism is suspected, to position the air superior to the right ventricular outlet and thus minimize risk of systemic embolization [7]. However, if air is suspected to have entered the pulmonary venous circulation or where the entry port is unknown, it is preferable to maintain the patient in a supine position, to avoid the risk of increased arterial pressure, which could further propel the air emboli, as well as aggravate brain edema secondary to existing cranial air emboli [7].

Definitive treatment for CAAE involves measures to increase arterial oxygen partial pressure (PaO_2) through high flow 100% FiO_2 or hyperbaric oxygen therapy [13]. Hyperbaric oxygen improves cerebral perfusion through three proposed mechanisms. First, as gas volume is inversely proportional to gas pressure (Boyle's law), increasing partial pressure decreases air emboli volume, facilitating the passage of air trapped in the capillary bed [8]. Second, increased PaO_2 lowers the vascular partial pressure of nitrogen in the cerebral circulation, promoting diffusion of nitrogen from the air emboli into the circulation and decreasing emboli volume (Fick's law: movement from high to low concentration proportional to the partial pressure gradient) [11]. Nitrogen is more likely than oxygen to persist in circulation and resist absorption because it is not metabolized or bound by hemoglobin. Third, higher partial pressures in the circulatory system can increase oxygen delivery to the distal ischemic tissue via collaterals. When hyperbaric oxygen is unavailable or the patient's condition does not permit transfer to a hyperbaric chamber, supplemental normobaric oxygen with 100% FiO_2 should be administered [7]. Timing of hyperbaric oxygen treatment should be prioritized, similar to embolic strokes where thrombolytic therapy needs to be administered within hours of the event; however, some case reports have demonstrated improvement even after delayed treatment [5].

PREVENTION

Various mechanisms have been suggested for the formation of CAAE during invasive bronchoscopy and therefore preventative strategies can be pursued in an attempt to mitigate the risk. For procedures involving gas, lower gas flow is recommended as air emboli has been correlated with the rate of gas flow [3]. To limit intra-procedural pulmonary pressures, where feasible, practitioners should minimize positive pressure ventilation as well as oxygen insufflation though the bronchoscope channel [13]. Further, deepening sedation to limit peri-procedural coughing, and refraining from wedging or complete occlusion of the bronchial tree can limit elevating pressures distal to the scope [13].

Referring to our experience, in the first two cases, both involving laser treatment, clear imaging evidence supported the diagnosis of CAAE; however, in neither case was hyperbaric oxygen pursued because of the patient's rapid deterioration. In the latter three cases, the patients did receive hyperbaric oxygen treatment and in two cases exhibited neurological improvement; however, direct causality cannot be inferred given the lack of definitive imaging evidence of CAAE. Rather the improvement may have been coincidental. TIA or mild strokes can be self-limiting and improve with the passage of time without directed treatment. Where CT imaging confirmed the presence of air embolism, in all cases the patient did not survive, implying that the severity of the patient's condition may be correlated with the presence of imaging confirmation of CAAE.

In the 23 published case reports identified, only 10 were treated with hyperbaric oxygen therapy, of which 4 (40%) improved neurologically post-treatment. Conversely, 13 cases were not treated with hyperbaric oxygen therapy, of which 10 (77%) improved neurologically. As such, causation cannot be implied by neurological improvement from hyperbaric oxygen therapy. Moreover, air emboli after TBLB is rare and as such often initially unrecognized; the time from presentation to hyperbaric oxygen therapy generally exceeds hours, potentially past the therapeutic window, which may be as narrow as 4-6 hours [11]. Nonetheless, while it is difficult to draw conclusions from the sparse data, given that prospective trials for hyperbaric oxygen therapy are neither feasible nor ethical, treatment with hyperbaric oxygen remains the standard of care treatment when CAAE is clinically suspected.

CONCLUSIONS

Although CAAE complications are uncommon in interventional bronchoscopy, the associated morbidity and mortality are substantial. In the presence of new onset neurological symptoms, hemodynamic instability, or impaired consciousness following interventional pulmonary procedures, CAAE should be included in the differential diagnosis. In these settings, practitioners should maintain a high index of suspicion for CAAE to facilitate early recognition and initiate hyperbaric oxygen therapy promptly, with or without corroborating imaging evidence, as the potential for neurologic improvement justifies the effort.

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Capsule

Safety and immunogenicity of an rVSV Lassa fever vaccine candidate

In this phase 1, double-blind trial conducted in the United States and Liberia, **Malkin** and co-authors randomly assigned healthy adults (18–50 years of age) to receive rVSVΔG-LASV-GPC or placebo intramuscularly. A total of 114 adults were enrolled. No serious vaccine-related adverse events were reported. The vaccine caused minimal local reactions and dose-dependent, mild-to-severe early-onset systemic reactogenicity events that were transient. No hearing loss was detected. All doses induced robust long-lasting cellular and humoral (binding and neutralizing) responses that cross-reacted against common LASV lineages. No infectious vaccine virus particles were found in plasma, urine, or saliva.

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