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CRITICAL CARE AND RESUSCITATION

CLINICAL CASE

Cardiac Arrest From Sulfur Hexafluoride Contrast Anaphylaxis After Prior Perflutren Hypersensitivity

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ABSTRACT

BACKGROUND Ultrasound-enhancing agents (UEAs) are generally considered safe, with severe reactions exceptionally rare. Cross-reactivity between agents remains poorly understood.

CASE SUMMARY A 62-year old man with prior hypersensitivity to perflutren lipid microspheres contrast agent developed anaphylaxis with pulseless electrical activity arrest immediately after administration of sulfur hexafluoride lipid microspheres contrast agent. After resuscitation, return of spontaneous circulation occurred within 2 minutes. An elevated tryptase level confirmed mast cell activation.

DISCUSSION Current guidelines support the use of sulfur hexafluoride lipid microspheres in patients with hypersensitivity to perflutren lipid microspheres given an absence of established cross-reactivity between contrast agents. This case underscores the potential for life-threatening anaphylactic reactions to UEAs, even in patients with prior documented tolerance to related formulations.

TAKE-HOME MESSAGES This is to our knowledge the first reported case of sulfur hexafluoride lipid microspheres anaphylaxis resulting in cardiac arrest in a patient with prior hypersensitivity to perflutren lipid microspheres. Clinicians should anticipate cross-sensitization between UEAs and maintain immediate access to resuscitation measures.
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HISTORY OF PRESENTATION

A 62-year old man with a history of coronary artery disease (CAD) status post percutaneous coronary intervention, hypertension, hyperlipidemia, and asthma presented with 1 week of exertional dyspnea and worsening chest pressure. Upon arrival, his vital signs were within normal limits, and physical examination was unremarkable.

TAKE-HOME MESSAGES

- Anaphylaxis induced by sulfur hexafluoride lipid microspheres resulted in cardiac arrest in a patient with prior hypersensitivity to perflutren lipid microspheres.
- Clinicians should anticipate cross-sensitization between UEAs and maintain immediate access to resuscitation measures.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CARPA = complement activation-related pseudoallergy

CPR = cardiopulmonary resuscitation

IgE = immunoglobulin E

PEA = pulseless electrical activity

PEG = polyethylene glycol

TTE = transthoracic echocardiography

UEA = ultrasound-enhancing agent

On the day of the arrest, the patient was undergoing transthoracic echocardiography (TTE) for cardiac ischemia evaluation. Given a prior adverse drug reaction to perflutren lipid microspheres, sulfur hexafluoride lipid microspheres was selected as the contrast agent. Immediately after injection of sulfur hexafluoride lipid microspheres, the patient developed facial flushing, tongue and lip swelling (angioedema), hypotension, and severe respiratory distress. An erythematous rash was present, involving the abdomen and extending across the upper torso. A rapid response team was called for respiratory arrest and flushing. Within 1 minute of sulfur hexafluoride lipid microspheres administration, the patient progressed to pulseless electrical activity (PEA) arrest.

PAST MEDICAL HISTORY

The patient had a history of CAD with left heart catheterization 1 year prior revealing severe 90% mid-left anterior descending artery stenosis and 95% ramus intermedius stenosis, both successfully treated with drug-eluting stents. Residual disease included 20% distal left main artery, 40% to 50% proximal-to-mid right coronary artery, and 30% to 50% left circumflex artery stenosis. Other comorbidities included hypertension, hyperlipidemia, obstructive sleep apnea, benign prostatic hyperplasia, and asthma.

Previous contrast exposures included a TTE with perflutren lipid microspheres 1.5 mL, which had been tolerated without adverse events, followed by a limited stress echocardiogram with perflutren lipid microspheres 1.5 mL, which caused severe lower back pain and rigors, necessitating early study termination. Multiple iodinated contrast (iopamidol/Isovue-370) studies, including cardiac catheterizations and computed tomography angiography, had been tolerated with only minor burning sensations upon administration. The patient had no prior angioedema and only spring allergies. He had received the Moderna and Pfizer mRNA COVID-19 vaccinations in 2021 and 2022, respectively. Home medications were reviewed and included amlodipine 2.5 mg, aspirin 81 mg, atorvastatin 40 mg, ezetimibe 10 mg, metoprolol succinate XL 50 mg, fluticasone 50 μg, fluticasone furoate-vilanterol 200-25 μg, ipratropium-albuterol 0.5 to 2.5 mg/3 mL, and tamsulosin 0.4 mg.

DIFFERENTIAL DIAGNOSIS

The acute presentation of facial flushing, angioedema, respiratory distress, hypotension, rash, and PEA arrest led to consideration of anaphylaxis to ultrasound-enhancing agents (UEAs), acute coronary syndrome, pulmonary embolism, hereditary angioedema, and acute asthma exacerbation.

INVESTIGATIONS

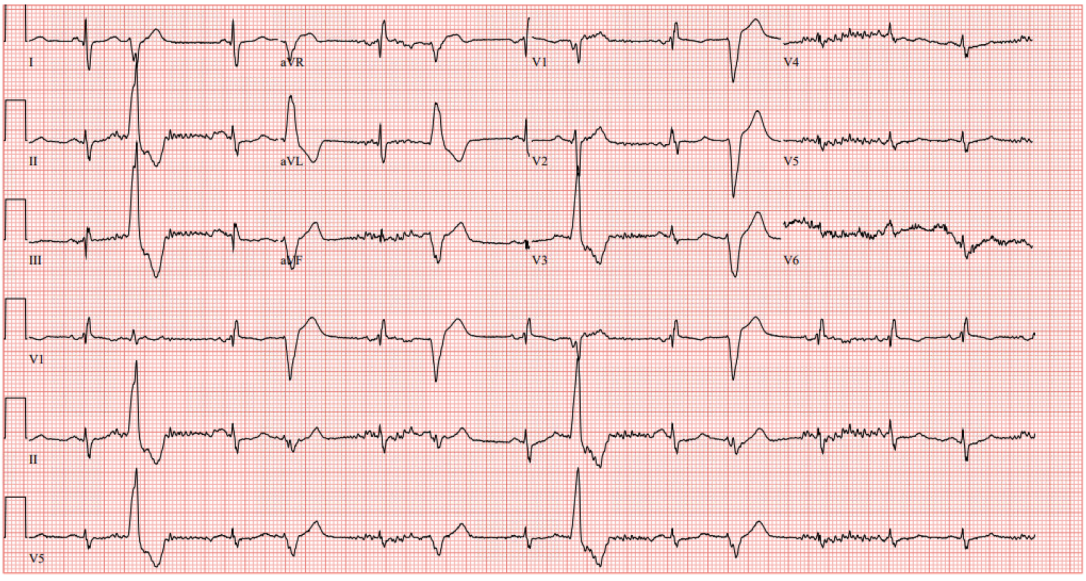
Laboratory evaluation revealed a markedly elevated serum tryptase level of 26.3 ng/mL immediately after the event, which normalized to 4.4 ng/mL at 24 hours, confirming systemic mast cell activation. Complement studies were performed to exclude hereditary angioedema and demonstrated normal C1 esterase inhibitor antigen (34 mg/dL) and function (>105%), with low C4 (9 mg/dL) and C1q (9.3 mg/dL) levels. Coronary angiography revealed stable CAD with patent stents compared with the prior left heart catheterization. Postresuscitation electrocardiogram

VISUAL SUMMARY Timeline of the Case

Event	Time	Clinical Details	Outcome
Isovue-370 contrast	May 2024	LHC, 337 mL	Mild burning sensation
Perflutren lipid microspheres contrast: first exposure	May 2024	TTE, 1.5 mL	No reaction
Perflutren lipid microspheres contrast: second exposure	January 2025	Stress echocardiogram, 1.5 mL	Severe back pain, rigors, study terminated
Sulfur hexafluoride lipid microspheres contrast exposure	Day 0	TTE, 2.0 mL	Facial flushing, respiratory distress, rash, angioedema, PEA arrest
CPR initiated	<1 min	Intravenous epinephrine, norepinephrine, steroids, antihistamines, fluids	ROSC after 2 min
ICU admission	Day 0	Supportive care	Stabilization
Isovue-370 contrast	Day 0	CT angiography chest, premedication not required, 80 mL	Severe burning sensation
	Day 5	LHC, premedicated, 80 mL	Stable CAD, no reaction

CAD = coronary artery disease; CPR = cardiopulmonary resuscitation; CT = computed tomography; ICU = intensive care unit; LHC = Left heart catheterization; PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; TTE = transthoracic echocardiography.

FIGURE 1 Electrocardiogram Conducted 30 Minutes After PEA Arrest



Electrocardiogram demonstrates normal sinus rhythm with frequent premature ventricular complexes but no clear dynamic changes compared to prior studies. PEA = pulseless electrical activity.

and cardiac enzymes were unremarkable. The significant elevation and subsequent normalization of tryptase levels, combined with the acute clinical presentation, confirmed systemic mast cell activation consistent with anaphylaxis.

MANAGEMENT

Immediately after the onset of anaphylaxis and PEA arrest, the patient received cardiopulmonary resuscitation (CPR), including 2 rounds of chest compressions and rescue breathing. Intravenous epinephrine was administered (10 μg, then 30 μg), followed by continuous infusion. Norepinephrine infusion was initiated for refractory hypotension. Additional interventions included intravenous methylprednisolone (125 mg), diphenhydramine (50 mg), famotidine (20 mg), and 2 L of lactated Ringer's solution.

OUTCOME AND FOLLOW-UP

Return of spontaneous circulation was achieved within approximately 2 minutes of CPR. The patient was lethargic after return of spontaneous circulation and continued to have angioedema and respiratory distress with associated muffled voice. A few minutes after resuscitation, he developed a wide-complex tachyarrhythmia, which was treated with 100 mg of intravenous lidocaine. An electrocardiogram approximately 30 minutes after the PEA arrest revealed no clear dynamic changes compared with prior examinations (Figure 1). Following stabilization, the patient was transferred to the intensive care unit, where he was weaned off the norepinephrine infusion within 6 hours after PEA arrest.

On the same day, the patient underwent computed tomography angiography of his chest with administration of 80 mL of iodinated contrast (Isovue-370) for evaluation of pulmonary embolism. Immediately after contrast administration, he reported a severe burning sensation and a feeling that he could "breathe fire," more intensely than during prior iodinated contrast exposures. No additional symptoms were noted. A formal allergy consultation confirmed severe anaphylactic reaction to sulfur hexafluoride lipid microspheres, prior mild hypersensitivity reaction to perflutren lipid microspheres, tolerance of iodinated contrast agents, and exclusion of hereditary angioedema given lack of prior isolated angioedema episodes and normal complement studies. The patient underwent successful left heart catheterization 5 days later with appropriate premedication (Prednisone 50 mg oral given 13 hours, 7 hours and 1 hour prior; diphenhydramine 50 mg oral given 1 hour prior, and 10mg montelukast given morning of the left heart catheterization), revealing patent stents and stable coronary anatomy, with a fractional flow reserve of 0.81. The contrast agent (Isovue-370, 80 mL) was tolerated with no reaction.

The patient was stable for discharge home 9 days after the PEA arrest, with pulmonary follow-up for further outpatient dyspnea work-up.

After discharge, the patient was initiated on continuous positive airway pressure therapy for severe obstructive sleep apnea (supine AHI 137), which he tolerated well with significant improvement in exertional capacity and daytime fatigue. His asthma control was optimized with adjustment of his inhaled corticosteroid/long-acting beta-agonist regimen. At follow-up, the patient reported marked improvement in his dyspnea, attributed to successful treatment of his sleep apnea and improved asthma control rather than cardiac etiology.

DISCUSSION

To our knowledge, our case represents the tenth reported instance in the literature of anaphylaxis induced by sulfur hexafluoride lipid microspheres and the first reported case resulting in PEA cardiac arrest in a patient with prior hypersensitivity to perflutren lipid microspheres, illustrating potential cross-reactivity between different UEAs. This occurrence runs counter to current guideline recommendations that support sulfur hexafluoride lipid microspheres use in patients with prior hypersensitivity to perflutren lipid microspheres given the absence of previously recognized cross-reactivity between agents.[1]

The incidence of hypersensitivity reactions to UEAs is very low. In a recent multicenter analysis from the Mayo Clinic and other U.S. health systems, the incidence of severe hypersensitivity to sulfur hexafluoride lipid microspheres (defined as cardiopulmonary involvement) was 0.0848%, and critical reactions (loss of consciousness, pulselessness, or ST-segment elevation) occurred in 0.0330% of administrations, with intercenter variability (severe: 0.0755% to 0.1093%; critical: 0.0293% to 0.0525%).[2] For perflutren lipid microspheres, the reported incidence of severe hypersensitivity is even lower at 0.0114%, with critical reactions in 0.0010% of administrations.[2] Consistent with these data, the American Society of Echocardiography estimates the overall risk of life-threatening reactions to UEAs at ~0.01% (1 in 10,000),[1] while the American Institute of Ultrasound in Medicine reports serious anaphylactoid reactions in 0.006% to 0.01%.[3] A recent systematic review identified only 4 prior cases of sulfur hexafluoride lipid microspheres-induced anaphylaxis affecting patients aged 47 to 67 years, none with pre-existing drug allergies,[4] with <30 other cases reported in the literature (**Table 1**). The severity of reactions varied from respiratory symptoms to cardiac arrest, with our case requiring CPR representing one of the most severe presentations.

Unlike typical anaphylactic reactions that require prior sensitization, our patient developed severe anaphylaxis on his first exposure to sulfur hexafluoride lipid microspheres. This pattern suggests cross-sensitization from prior perflutren lipid microspheres exposure or the presence of shared antigenic components between the 2 agents. The patient's clinical course—initial tolerance to perflutren lipid microspheres, a mild reaction on subsequent perflutren lipid microspheres exposure, and severe anaphylaxis with first-time sulfur hexafluoride lipid microspheres exposure—supports cross-reactivity. Although these agents have different core gases (perflutren vs sulfur hexafluoride), sulfur hexafluoride lipid microspheres and perflutren lipid microspheres share phospholipid shells and may contain common excipients, including polyethylene glycol (PEG), a compound increasingly recognized as a trigger of immunoglobulin E (IgE)-mediated reactions.[1] The main component of sulfur hexafluoride lipid microspheres is PEG-4000, a macrogol with molecular weights ranging from 200 to 35,000 g/mol, and hypersensitivity to higher-molecular weight PEGs has been associated with type I IgE-mediated reactions, likely accounting for the severity of the anaphylaxis observed in this case.[5,6]

Complement activation-related pseudoallergy (CARPA), a non-IgE-mediated reaction, is another important consideration. Although CARPA can produce anaphylactoid presentations to lipid-based and particulate agents, several features of this case favor an IgE-mediated mechanism. The patient had prior sensitizing exposures (adverse reaction to perflutren lipid microspheres) with escalation to a more severe event on exposure to sulfur hexafluoride lipid microspheres, a pattern more consistent with IgE-mediated hypersensitivity than with CARPA, which typically occurs on first exposure and often attenuates with repeat dosing.[7] A marked rise (26.3 ng/mL) and subsequent normalization (4.4 ng/mL) of serum tryptase provides objective evidence of systemic mast cell degranulation. Moreover, the observed complement profile (low C1q and C4) is not the classic anaphylatoxin signature of CARPA (elevated C3a/C5a or sC5b-9); however, lack of anaphylatoxin measurements limits definitive exclusion of CARPA.

Another diagnostic consideration is Kounis syndrome, or allergic acute coronary syndrome, in which mast cell degranulation during anaphylaxis precipitates coronary vasospasm or plaque rupture.[8] Our patient's history of CAD and elevated tryptase level are consistent with the type of immune activation

TABLE 1 Summary of Previously Reported Cases of Anaphylaxis Induced by Sulfur Hexafluoride Lipid Microspheres

First Author (Year)	No. of Anaphylactic Reactions	Publication Type	Description
Coudray et al (2017)[10]	1	Case report	62-year-old male; full recovery after ICU admission; treated with epinephrine, steroids, antihistamines, and fluids
Ionescu (2009)[11]	1	Case report	55-year-old male; home next day after CCU monitoring; treated with atropine, steroids, antihistamines, fluids, vasopressor, and anticonvulsant
Levano et al (2012)[12]	1	Case report	39-year-old female; recovered after ICU intubation and vasopressors; treated with fluids, steroids, antihistamines, norepinephrine
Solivetti et al (2012)[13]	1	Case report	45-year-old female; recovered after overnight observation; treated with oxygen, steroids, antihistamines, and plasma expanders
Calvo et al (2006)[14]	1	Case report	42-year-old male; full recovery after cardiac arrest; treated with advanced cardiopulmonary resuscitation
Steinhauer et al (2023)[15]	1	Case report	49-year-old female; full recovery after repeat CPR and advanced cardiac support; treated with epinephrine, steroids, antihistamines, and mechanical circulatory support
Mikhail et al (2023)[4]	1	Case report	Early 50s male; full recovery after ICU monitoring; treated with oxygen, steroids, antihistamines, and bronchodilator
Olson et al (2018)[16]	1	Case report	63-year-old male; full recovery after cardiac arrest and ICU care; treated with epinephrine, steroids, antihistamines, bronchodilators, and supportive ventilation
Mansour et al (2022)[17]	1	Case report	Early 50s male; full recovery after ICU monitoring; treated with oxygen, steroids, antihistamines, and bronchodilator
Kerber and Li (2022)[18]	1	Case report	47-year-old female; full recovery after ICU care; treated with IM and IV epinephrine, steroids, antihistamines, and oxygen
Longhino et al (2024)[19]	1	Case report	67-year-old male; full recovery after cardiac arrest; treated with CPR, steroids, antihistamines, airway support, and sedative
Levy et al (2025)[20]	1	Case report	39-year-old female; discharged after 8 days of ICU and cardiac support; treated with multiple epinephrine doses, steroids, antihistamines, vasopressors, fluids, dobutamine, and intra-aortic balloon pump.
Shang et al (2023)[21]	13	Retrospective safety cohort	Multicenter registry (>460,000 doses) with extremely low rate (~0.001%) of serious anaphylaxis, all patients treated and recovered
Li et al (2024)[22]	3	Retrospective safety cohort	Single-center retrospective cohort (83,778 examinations) found rare serious anaphylaxis (0.006%); all affected patients recovered after allergy and shock management
Li et al (2023)[23]	3	Retrospective safety cohort	Single-center cohort (49,100 examinations) showed very rare severe AEs (0.014%), all patients recovered

Summary of published case reports and retrospective safety cohorts describing anaphylactic reactions following administration of sulfur hexafluoride lipid microspheres as of November 2025. All cases resulted in survival after prompt emergency therapy.

AE = adverse event; CCU = cardiac care unit; CPR = cardiopulmonary resuscitation; ICU = intensive care unit; IM = intramuscular; IV = intravenous.

that can underlie Kounis syndrome. However, the absence of dynamic electrocardiographic changes, normal troponins, and angiographically stable coronary anatomy argue against this mechanism as the primary cause of cardiac arrest.

Of note, the American Society of Echocardiography has reported an increased rate of adverse reactions to UEAs coinciding with the widespread use of PEG-containing SARS-CoV-2 mRNA vaccines.[9] In their analysis, patients experiencing adverse reactions to sulfur hexafluoride lipid microspheres were statistically more likely to have received an mRNA vaccine, particularly the Moderna formulation.[2] Our patient's history included completion of a Moderna mRNA vaccination series in 2021 and a Pfizer booster in 2022. While causality cannot be established, prior immune priming through PEG-containing vaccines may represent an additional sensitization pathway that could have contributed to the severity of this reaction.

CONCLUSIONS

Severe anaphylaxis may occur with UEAs, even in patients with prior documented tolerance to related agents. Cross-reactivity, likely mediated by PEG via a type I IgE-mediated hypersensitivity mechanism, has been proposed as an underlying cause. Accordingly, vigilant monitoring and immediate readiness for resuscitation are imperative during contrast administration.

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KEY WORDS **chest pain, contrast agent, echocardiography, electrocardiogram**