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# Anaphylactic shock and cardiac arrest after intravenous injection of sulphur hexafluoride SonoVue

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## SUMMARY

A male patient in his early 60s was referred to the cardiology department for evaluation of a persistent apical ventricular thrombus following a myocardial infarction. Transthoracic echocardiography could not rule out the presence of an apical thrombus, leading to the intravenous administration of the contrast agent sulphur hexafluoride (SonoVue). The patient quickly exhibited signs of anaphylaxis accompanied by haemodynamic shock, resulting in cardiac arrest. He was successfully resuscitated with no significant secondary neurological impairment. According to the European Medicines Agency, anaphylactic reactions to the contrast agent sulphur hexafluoride (SonoVue) occur in approximately 1 in 10 000 cases. To our knowledge, this represents the first case of hypersensitivity to sulphur hexafluoride (SonoVue) confirmed by positive in vitro testing.

## BACKGROUND

In about one-third of patients undergoing stress echocardiography, the exam does not yield conclusive diagnostic images (>30%), primarily due to obesity or lung disease.[1 2] Contrast agents are employed to increase blood echogenicity, aiding in the visualisation of the left ventricular endocardial border. Their use is recommended in clinical guidelines when two or more contiguous segments of the left ventricle are not clearly visible during stress echocardiography.[3 4] SonoVue, the most commonly used agent, consists of sulphur hexafluoride microbubbles coated with phospholipids and various excipients (macrogol 400, distearoylphosphatidylcholine, dipalmitoylphosphatidylglycerol sodium, palmitic acid and 0.9% sodium chloride), administered via intravenous injection. SonoVue has a favourable safety profile, with a very low incidence of serious adverse events (ranging from 0.008% to 0.9%). According to the European Medicines Agency (EMA), anaphylactic reactions have been reported in approximately 1 in 10 000 cases, with a few severe reactions documented in the literature.[5–9] However, no comprehensive allergy studies have been conducted to distinguish hypersensitivity to the active substance from hypersensitivity to the excipients. Most cases in the literature attribute hypersensitivity to the excipient macrogol (also known as polyethylene glycol or PEG), an ingredient also present in certain mRNA vaccines against SARS-CoV-2.

## CASE PRESENTATION

A male patient in his early 60s with a history of ischaemic cardiomyopathy, prior cardiac arrest (5 years ago) and moderate anoxic encephalopathy was hospitalised following an anterior myocardial reinfarction. Intrastent stenosis in the left anterior descending artery was quickly reperfused, yet left ventricular systolic function remained severely compromised, with an ejection fraction of 25%. One month later, transthoracic echocardiography (without contrast) revealed a 20×15 mm apical thrombus, leading to the initiation of therapeutic anticoagulation with rivaroxaban and clopidogrel. Two months later, he was hospitalised for dehydration and hypernatremia caused by worsening dyskinetic cerebral palsy, which impeded adequate oral fluid intake. A brief interruption of anticoagulation was therefore considered to allow for Botox injection to mitigate dyskinesia. An apical artefact prevented echocardiographic confirmation of the previously diagnosed apical thrombus. Consequently, the contrast agent SonoVue was administered for diagnostic purposes. Three minutes following intravenous administration of 2 ml of SonoVue, the patient developed a rash on his chest and abdomen. Assessing the patient was challenging due to his inability to communicate verbally, although comprehension seemed unimpaired. The patient subsequently developed respiratory failure with stridor, followed by haemodynamic instability and cardiac arrest. He had no known history of allergies and, to our knowledge, had never previously been exposed to SonoVue.

## INVESTIGATIONS

The serum tryptase level, measured 2 hours after the onset of symptoms, was elevated at 16 µg/L (reference range: 0–11.4 µg/L), which is consistent with anaphylactic shock. Six weeks later, the baseline serum tryptase level was within the normal range (8 µg/L), ruling out systemic mastocytosis or familial/genetic hypertryptasaemia. Due to the severity of the reaction, no skin tests were performed to protect the patient. Instead, a basophil activation test (BAT) was conducted. BAT is an in vitro cellular test in which the patient's blood is initially incubated with the suspected allergen. If the test is positive, basophils are activated, indicating an IgE-mediated type I hypersensitivity reaction (Gell and Coombs classification) and express specific surface markers, such as CD63. The degree of CD63 upregulation is then quantified via flow cytometry. In our case, BAT was positive for SonoVue (sulphur hexafluoride and excipients like macrogol/PEG 2000) but negative for macrogol/PEG 2000 alone.

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## DIFFERENTIAL DIAGNOSIS

The diagnosis of anaphylactic shock due to SonoVue is well-supported by the temporal relationship between drug administration and symptom onset, the typical clinical presentation, elevated serum tryptase levels and positive in vitro test results. Given the structure of SonoVue, the excipient macrogol would typically be suspected as the causative agent, given the frequency of macrogol-induced reactions reported in the literature. However, in our case, macrogol does not appear to be involved, as the BAT, an in vitro test with relatively high sensitivity,[10] was negative. Nonetheless, anaphylactoid or non-IgE-mediated mast cell activation cannot be entirely ruled out. Currently, no specific tests are available to assess non-IgE-mediated mast cell activation.

## TREATMENT

The patient was initially treated with antihistamines and corticosteroids. On the first signs of respiratory failure, he received oxygen, intravenous fluids and intravenous epinephrine in accordance with standard protocol. Following cardiac arrest, standard cardiopulmonary resuscitation (CPR) measures were initiated, including the administration of epinephrine and amiodarone. The first recorded rhythm showed pulseless electrical activity, which was subsequently followed by ventricular tachycardia, requiring two immediate electrical defibrillations.

## OUTCOME AND FOLLOW-UP

After 25 min of CPR, during which there was 0 min of no-flow time and 25 min of low-flow time, the patient regained spontaneous circulation and was admitted to the intensive care unit (ICU). After 5 days, the patient showed favourable progress with no sustained neurological damage and was subsequently transferred to the general medical ward.

## DISCUSSION

Ultrasound contrast media are characterised by a safe profile and high diagnostic value. However, this case illustrates that rare but serious side effects, such as anaphylaxis and cardiac arrest, may occur. SonoVue is contraindicated in patients with known hypersensitivity to sulphur hexafluoride or any of its excipients, although such cases are rare (1 in 10 000).[5 11] Our patient had no history of allergy, making this reaction unfortunately unpredictable. Prompt emergency treatment was critical for the patient's survival. When using SonoVue, certain precautions are recommended by the US Food and Drug Administration (FDA) and the EMA. These include having emergency equipment and trained personnel immediately available during and at 30 min after administration. Close medical supervision of the patient, with monitoring of vital signs, is warranted during and for at least 30 min after the infusion, especially in high-risk patients. Other contraindications to SonoVue include current or recent acute coronary syndrome (>7 days), acute heart failure, severe arrhythmias, right-to-left cardiac shunts, severe pulmonary hypertension (pulmonary artery pressure>90 mmHg), uncontrolled systemic hypertension, respiratory distress syndrome, pregnancy and lactation. The use of alternative contrast agents, such as Definity or Optison, has been approved by the FDA for acute cardiac conditions due to growing evidence of their safety and favourable risk-benefit profile. Regarding anaphylactic reactions, several cases of allergic reactions due to macrogol/PEG hypersensitivity have been reported, although only a few case studies are found in the literature. The first case published in 2012[12] involved a 39-year-old woman with liver disease who underwent abdominal ultrasound and developed rapid shock after SonoVue administration. This was her first exposure to SonoVue. Allergy testing, including skin testing, was negative, but anaphylaxis could not be ruled out due to the unknown sensitivity of the test. Notably, no in vitro tests or tests with excipients were performed in this case. The second case, also published in 2012,[7] involved a 45-year-old woman with no history of cardiac disease, but unfortunately, no allergy tests were conducted. More recently, a case involving a 60-year-old male, who had a follow-up 6 months after endovascular repair of an aortic aneurysm, was reported.[8] Allergy assessment included only skin prick tests, all of which were negative. Additionally, N. Oyarzabal *et al*[6] described a case of proven allergy to the preservative macrogol, which had positive skin tests and negative BAT.

Our investigations confirmed a proven in vitro hypersensitivity to sulphur hexafluoride (SonoVue) with no reaction to the excipient macrogol. This suggests a hypersensitivity to sulphur hexafluoride itself or to macrogol only when structurally associated with sulphur hexafluoride within a phospholipid shell, which differs structurally from macrogol alone. It is noteworthy that some high molecular weight forms of macrogol (eg, macrogol 2000 to 8000) tend to promote IgE cross-linking at the mast cell surface, which is one step in IgE-mediated anaphylaxis. It remains questionable why symptoms occurred after the first exposure to SonoVue in some of the reported cases. One argument is that some patients may have been exposed to SonoVue in the past without such records in their medical history. In instances of proven anaphylaxis to macrogol, pre-sensitisation is plausible, as many parenteral drugs contain PEG, leading to potential sensitisation from prior exposures. Some authors have proposed mechanisms such as direct mast cell activation, complement activation, increased serotonin release and inhibition of enzymes like cholinesterase, similar to other contrast media.[8]

To our knowledge, this case represents the first report of an anaphylactic reaction to SonoVue (sulphur hexafluoride+macrogol 4000) demonstrated through in vitro testing. It highlights the utility and safety of in vitro testing in the allergy workup for severe reactions, as skin tests can sometimes lead to severe systemic reactions. Furthermore, this case underscores the importance of preventive measures when using contrast media in echocardiography. Although SonoVue is a highly useful and commonly used agent in clinical practice, a thorough clinical history and training to manage potentially life-threatening adverse events are essential.

### Learning points

- Ultrasound contrast media have a safe profile and high diagnostic value; however, rare but serious side effects, such as anaphylaxis and cardiac arrest, can occur.
- When using contrast agents, it is recommended to have emergency equipment and trained personnel immediately available during and after injection, particularly in ambulatory settings.
- The basophil activation test is a safe in vitro hypersensitivity test useful in allergy workups for severe reactions, minimising the potential risks associated with skin tests.
- This case represents the first report of an anaphylactic reaction to SonoVue (sulphur hexafluoride+macrogol 4000), as demonstrated by in vitro testing, rather than to the excipient alone.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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