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Recurrent anaphylaxis during cardiac catheterization due to ethylene oxide

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TO THE EDITOR

Ethylene oxide (EtO) is a low molecular weight alkylating agent that is toxic and lethal to microbes. EtO is used to sterilize dialysis membranes, catheters, infusion sets, and other medical devices that cannot undergo high temperature steam sterilization [1, 2]. Previous reports have described IgE-mediated immediate hypersensitivity reactions in patients sensitized to residual EtO in hemodialysis filters and tubing [3, 4]. Others have reported allergic reactions to EtO in patients with spina bifida, a population with extensive exposure to EtO in the setting of repeated surgical procedures [1, 5]. To date, there are no reports of patients with EtO-mediated anaphylaxis in the setting of cardiac catheterization. Here, we describe a 71-year-old male with peri-procedural anaphylaxis during cardiac catheterization using angiocatheters sterilized with EtO.

The patient had a history of coronary artery disease, diabetes mellitus, spinobulbar muscular atrophy, allergic rhinitis, and asthma. One year prior to presentation, he underwent a PET myocardial perfusion stress test for evaluation of progressive fatigue which ultimately led to left heart catheterization (LHC) and subsequent placement of one drug eluting stent to his left circumflex artery. In the setting of recurrent fatigue with minimal exertion, he underwent LHC following an abnormal nuclear stress test. The patient had tolerated three previous LHCs without issue.

A left ventriculogram was performed using a 6-French Angled pigtail catheter (Boston Scientific, Marlborough, MA) in the right femoral artery with 40 mL of iohexol (Omnipaque) radiocontrast. Minutes after contrast injection, the patient developed hypotension (aortic pressure of 56/30), relative bradycardia (heart rate of 64), diffuse

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pruritus, flushing and abdominal rash. The procedure was terminated early and the patient treated intravenously (IV) with dopamine (up to 20 mcg/kg/min), 1 mg atropine, and 50 mg methylprednisolone. Within 15 minutes, blood pressure and heart rate normalized, dopamine was discontinued and the patient transferred to the cardiac intensive care unit (CICU). The presumed diagnosis was non-IgE-mediated radiocontrast-induced anaphylaxis and the patient was rescheduled for repeat LHC with steroid and antihistamine premedication (Table 1).

Two days later, the patient underwent repeat LHC and was pre-medicated with prednisone 50 mg, 13, 7, and 1 hour prior to the procedure and IV diphenhydramine 1 hour prior. Within seconds after infusion of 1 ml iohexol radiocontrast through a Boston Scientific angiocatheter in the right femoral artery, the patient reported right leg pruritus that quickly progressed to diffuse full body pruritus. He was again hypotensive and bradycardic, requiring early termination of the procedure and CICU monitoring. He was discharged home the following day and referred to Allergy/Immunology for additional evaluation for radiocontrast allergy.

While the utility of skin testing for radiocontrast hypersensitivity is controversial, the negative predictive value of a negative test is high [6], and two weeks later, skin prick testing (SPT) and intradermal testing (1:1000, 1:100, 1:10 dilutions) to iohexol and an alternative radiocontrast dye iodexanol (Visipaque) were negative. Iodexanol was recommended for subsequent LHCs in conjunction with premedication with corticosteroids and diphenhydramine.

Over the following month, the patient reported increasing fatigue and weakness despite intensified medical therapy. Repeat LHC was indicated and the patient was premedicated with prednisone every 6 hours starting 13 hours before LHC as well as IV methylprednisolone and IV diphenhydramine 1 hour prior to LHC. The patient received IV midazolam and fentanyl and local subcutaneous infiltration of the right thigh with lidocaine and a Boston Scientific angiocatheter advanced into the right femoral artery. Prior to the administration of any radiocontrast dye, the patient had severe anaphylaxis with diffuse pruritus, flushing, and hypotension. He was intubated due to hypoxia. He required dopamine, phenylephrine, atropine, and epinephrine before his hypotension resolved. After the patient was stabilized, LHC was completed using iohexol radiocontrast media and anticoagulation with heparin.

Since the patient's last episode of peri-LHC anaphylaxis occurred prior to radiocontrast infusion, other triggers of peri-procedure anaphylaxis were considered including medications, latex, skin disinfectant, and sterilizers used for medical equipment, i.e. EtO. According to bostonscientific.com, the Boston Scientific angiocatheters used for this patient's LHCs were made of intermediate polymers and linear elastic nitinol, contained hydrophilic or silicone coating, did not list latex as a product component, and were sterilized with EtO. Mast cell disorders were considered, but not supported by clinical history, and while tryptase was not assayed immediately following any of the three episodes of anaphylaxis, baseline tryptase checked 9 months after the last episode of anaphylaxis was 5.8 ng/ml (normal <11.5 ng/ml).

Subsequent SPT and intradermal testing (1:100 and 1:10 dilutions) to midazolam, fentanyl, and lidocaine were all negative. During the three episodes of peri-procedural anaphylaxis, the skin over the catheter insertion site had been disinfected with chlorhexidine gluconate prior to catheter insertion. However, skin prick and intradermal tests with chlorhexidine gluconate (5mg/ml for SPT and 0.002 mg/ml for intradermal testing) were negative making IgE-mediated chlorhexidine disinfectant allergy unlikely. Latex-specific serum IgE was <0.35 kU/L while EtO-specific IgE was highly elevated at 64.2 kU/L as measured by Phadia ImmunoCAP.

Basophil activation testing to EtO (EtO BAT) performed using the patient's plasma was positive, with greater than four-fold higher frequency of CD63+ activated basophils detected compared to EtO BAT performed with a healthy control subject's plasma (Figure 1). To perform EtO BAT, peripheral blood mononuclear cells (PBMCs) from a healthy donor were stripped of native IgE and sensitized for 16 hours with the patient's plasma or a negative control subject's plasma. Sensitized PBMCs were incubated with RPMI cell culture media, recombinant IL-3, and 1 microgram/ml EtO for 30 minutes, harvested, and stained with antibodies against HLA-DR, CD123, CD203c, CD63 and Lineage 1 (CD3, CD19, CD20, CD14, CD16, CD56) for flow cytometric analysis. EtO dissolved in dimethyl sulfoxide (DMSO) was purchased from Restek (Bellefonte, PA). DMSO made up no more than 0.2% of the total culture volume to minimize any adverse effects of DMSO alone on the PBMCs. EtO was stored at 4°C in a well ventilated research laboratory until use. Appropriate personal protective equipment, including eye and skin protection, was used at all times when handling EtO. Moreover, EtO was manipulated within a biological safety cabinet and tissue culture hood with vertical laminar flow and a HEPA filter. EtO likely reacted with methionine and cysteine residues in human serum albumin in the patient's plasma [7] and possibly in IL-3 to create molecules large enough to crosslink EtO-specific IgE bound to the basophil surface.

Preincubating patient plasma with 500 nM omalizumab prior to EtO BAT reduced the frequency of activated basophils by half (Figure 1). These studies suggest that IgE-mediated hypersensitivity to EtO was the etiology of this patient's recurrent episodes of peri-LHC anaphylaxis. We believe the patient was exposed to EtO through his previous left heart catheterizations with EtO-sterilized catheters and his EtO-sterilized drug eluting stent.

To our knowledge, this is the first report of recurrent IgE-mediated anaphylaxis to EtO-sterilized cardiac angiocatheters. The overall prevalence of IgE antibodies against EtO is unknown, although EtO-specific IgE antibodies could be detected in 13 out of 107 (12.1%) hemodialysis patients in one study [8] and 17 of 75 (23%) spina bifida patients in another [5]. Sensitization to EtO does not always correspond to IgE-mediated allergy to EtO. In most cases, EtO-sensitized patients never experience peri-procedural anaphylaxis despite exposure to EtO [1, 5]. EtO may haptenate human serum proteins, such as albumin, forming novel allergens that trigger immediate hypersensitivity responses [9]. Previous studies have shown positive SPT and significantly higher levels of serum IgE specific for EtO-altered human serum albumin in hemodialysis patients with a history of anaphylaxis during dialysis than in those without [3]. No FDA-approved commercially available SPT reagents exist to assess EtO allergy. EtO re-challenge may be impractical or unsafe.

If EtO allergy is suspected, avoidance of biomedical devices and catheters sterilized with EtO is advised. Steam-sterilized, gamma-irradiated, or hydrogen peroxide gas plasma-sterilized devices are possible alternatives [10]. Pretreatment with antihistamines and corticosteroids can be considered in EtO-allergic individuals who must undergo procedures with EtO-sterilized equipment, especially if the equipment is to be implanted as this may increase the risk of clinical reactions in sensitized patients [1]. Extensive flushing and saline irrigation can also be helpful [11], although it may increase the risk of microbial contamination [1]. Since using a non-EtO sterilized device is not always possible and it can be challenging to completely eradicate EtO from medical devices, there may be a role for combining the two approaches; extensively flushing EtO-sterilized equipment and also pretreating the EtO-allergic patient prior to procedure with antihistamines and corticosteroids. Notably, adding omalizumab, a monoclonal antibody against IgE, to this patient's EtO BAT diminished basophil degranulation in response to EtO (Figure 1). Thus, pretreatment with anti-IgE therapy (e.g. omalizumab) could also be considered and has been previously reported to mitigate IgE-mediated reactions to EtO [10].

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References

1. Bache S, Petersen JT, Garvey LH. Anaphylaxis to ethylene oxide - a rare and overlooked phenomenon? *Acta Anaesthesiol Scand*. 2011; 55(10):1279–82. [PubMed: 22092134]
2. Poothullil J, et al. Anaphylaxis from the product(s) of ethylene oxide gas. *Ann Intern Med*. 1975; 82(1):58–60. [PubMed: 1235763]
3. Grammer LC, et al. IgE against ethylene oxide-altered human serum albumin in patients with anaphylactic reactions to dialysis. *J Allergy Clin Immunol*. 1985; 76(3):511–4. [PubMed: 4031322]
4. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. *Br Med J (Clin Res Ed)*. 1986; 292(6530):1221–2.
5. Pittman T, et al. Ethylene oxide allergy in children with spina bifida. *J Allergy Clin Immunol*. 1995; 96(4):486–8. [PubMed: 7560659]
6. Caimmi S, et al. Clinical value of negative skin tests to iodinated contrast media. *Clin Exp Allergy*. 2010; 40(5):805–10. [PubMed: 20337646]
7. Chen L, et al. Chemical modifications of therapeutic proteins induced by residual ethylene oxide. *J Pharm Sci*. 2015; 104(2):731–9. [PubMed: 25407640]
8. Marshall C, et al. Ethylene oxide allergy in a dialysis center: prevalence in hemodialysis and peritoneal dialysis populations. *Clin Nephrol*. 1984; 21(6):346–9. [PubMed: 6467690]
9. Dolovich J, Bell B. Allergy to a product(s) of ethylene oxide gas: demonstration of IgE and IgG antibodies and hapten specificity. *J Allergy Clin Immunol*. 1978; 62(1):30–2. [PubMed: 307011]
10. Listyo A, et al. Severe anaphylactic shock due to ethylene oxide in a patient with myelomeningocele: successful exposure prevention and pretreatment with omalizumab. *A A Case Rep*. 2014; 2(1):3–6. [PubMed: 25612258]
11. Ansorge W, et al. Ethylene oxide in dialyzer rinsing fluid: effect of rinsing technique, dialyzer storage time, and potting compound. *Artif Organs*. 1987; 11(2):118–22. [PubMed: 3593041]

Clinical Implications

- This is the first report of peri-procedural anaphylaxis secondary to ethylene oxide in a patient undergoing cardiac catheterization.

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Figure 1.

A, Gating Strategy for Flow Cytometric Analysis of Ethylene Oxide Basophil Activation Test. Basophils were defined as HLA-DR⁻Lin⁻CD123⁺CD203c⁺. **B**, Frequency of CD63⁺ (activated) basophils. Healthy donor peripheral blood mononuclear cells stripped of native IgE and sensitized with patient or negative control plasma were incubated with ethylene oxide. In some experiments, omalizumab 500 nM was added to patient plasma.

Table 1

Time Course of Events and Diagnostic Workup

Time Course	Events	Test Results
Day 0	<ul style="list-style-type: none"> First episode of anaphylaxis during LHC following 40 ml Iohexol radiocontrast administered IV. Early termination of LHC IV dopamine, atropine, and methylprednisolone administered and symptoms resolve 	
Day 1	<ul style="list-style-type: none"> Allergy/Immunology inpatient consult Recommendations to pre-medicate patient with H1, H2 antihistamines, and corticosteroids prior to subsequent LHC 	
Day 2	<ul style="list-style-type: none"> 2nd episode of anaphylaxis following IV injection of 1ml iohexol during LHC despite pre-medication with antihistamines and corticosteroids Normal saline, dopamine, atropine, and methylprednisolone given; symptoms resolve 	
Day 16	<ul style="list-style-type: none"> Allergy/Immunology outpatient evaluation with SPT and intradermal testing to radiocontrast agents iohexol and iodexanol. 	SPT and intradermal tests to iohexol and iodexanol are negative
Day 47	<ul style="list-style-type: none"> 3rd Episode of anaphylaxis during LHC. Anaphylaxis occurs PRIOR to injection of iohexol contrast. Patient stabilized and LHC completed with iohexol radiocontrast. Allergy/Immunology Inpatient Consult recommendations include testing for latex IgE and outpatient follow up to evaluate for perioperative drug allergy 	Latex IgE <0.35 kUA/L
Day 132	<ul style="list-style-type: none"> Allergy/Immunology Outpatient evaluation with SPT and intradermal testing to periprocedural anesthetic agents fentanyl, lidocaine, midazolam 	SPT and intradermal tests to fentanyl, lidocaine, and midazolam are negative
Day 135	<ul style="list-style-type: none"> Serum ethylene oxide (EtO)-specific IgE assayed 	EtO IgE = 64.2 kUA/L
Day 307	<ul style="list-style-type: none"> EtO basophil activation test performed 	EtO BAT is positive
Day 309	<ul style="list-style-type: none"> Serum tryptase performed 	Tryptase is 5.8 ng/ml (normal <11.5 ng/ml)
Day 406	<ul style="list-style-type: none"> SPT and intradermal testing to chlorhexidine gluconate 	SPT and intradermal tests to chlorhexidine gluconate are negative

Abbreviations: BAT, basophil activation test; EtO, ethylene oxide; IgE, immunoglobulin E; ml, milliliters; IV, intravenous; SPT, skin prick test