

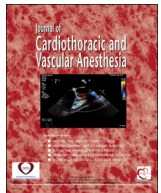
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Case Report

Deep Hypothermic Circulatory Arrest in a Patient with Cold-Induced Urticaria

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COLD-INDUCED URTICARIA (CIU), also known as acquired cold urticaria, is a syndrome characterized by the development of hives, localized swelling, swelling of the lips or tongue, and systemic reactions such as bronchospasm, hypotension, and shock in response to cold stimulation.¹⁻⁴ CIU affects 5.2% to 33% of individuals with chronic urticaria, depending on the climate and study involved, and 0.05% of the total population.⁵ Case reports of patients undergoing cardiac surgery with cardiopulmonary bypass can be grouped into the following 2 categories: patients undergoing normothermic cardiopulmonary bypass (36°-37°C)^{4,6,7} and patients undergoing hypothermic cardiopulmonary bypass.^{3,8-10} Patients who underwent hypothermia received preoperative treatment with regimens that often started days in advance after consultation with an allergist. The authors report a case of a 66-year-old woman with a medical history of CIU who underwent successful repair of an ascending aortic aneurysm using deep hypothermic circulatory arrest (DHCA) who did

not require consultation with an allergist or pretreatment before the day of surgery.

Case Presentation

A 66-year-old woman was scheduled for replacement of her ascending aorta and proximal aortic arch, with debranching of the innominate and left carotid arteries under DHCA. The patient's medical history was significant for smoking, high cholesterol, hypertension, stroke, seizure, preserved ejection fraction, eczema, and CIU. The patient had a fusiform ascending aortic aneurysm measuring 5.0 cm, aortic root dilation measuring 3.0 cm, and descending thoracic aortic aneurysm of 5.5 cm, all with interval growth from an evaluation 2 years prior. Repair of the ascending aortic aneurysm and aortic root were scheduled first, with staged repair of the descending aorta to follow at a later date.

The patient was diagnosed with CIU 34 years before the surgery. Initially, her symptoms included total body itching and rash after exposure to cold water or changes in temperature. She also experienced tongue swelling when she ate ice cream or drank cold beverages. She managed her symptoms by avoiding cold exposures and over time she experienced some reduction in her symptomatology. Before surgery her

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symptoms were limited to itching of her hands when in contact with cold objects (eg, a milk jug) or when exposed to cold winter temperatures.

The patient's history of CIU was documented on her preoperative assessment; however, her chart was not reviewed by an anesthesiologist until the day before surgery. On the day of surgery her history was verified and it was noted that the patient had not seen an allergist or been medicated for CIU for more than 5 years. After discussion with the surgeon, a plan was made to pretreat the patient with 100 mg of hydrocortisone, 50 mg of diphenhydramine, and 100 mg of ranitidine intravenously. One hour later a cold stimulation test was performed on the volar surface of the patient's forearm, which was nonreactive. The results were discussed with an allergist over the phone and the decision was made to proceed with the repair. Had the cold stimulation test elicited a lesion, the surgery would have been cancelled and a formal consultation with an allergist/immunologist would have taken place.

After induction of anesthesia, the patient was given 250 mg of methylprednisolone, 100 mg of ranitidine, and 50 mg of diphenhydramine intravenously. Prior to patient cooling, a low dose epinephrine infusion was initiated at 0.5 µg/min for its mast-cell-stabilizing effects. The patient did not have known coronary artery disease, and the plan was to stop the epinephrine if she became hypertensive. Intraoperatively, the patient underwent 135 minutes of cardiopulmonary bypass, including 93 minutes of cross-clamp time, and 47 minutes of DHCA. Antegrade cerebral perfusion was performed through the right axillary artery. During circulatory arrest the patient's core temperature ranged from 15.4° to 24.7° C, with an average temperature of 22.1° C. Before rewarming, the epinephrine infusion, which was paused during DHCA, was restarted and an additional 50 mg of intravenous diphenhydramine was administered. Diphenhydramine (25 mg every 12 h) and hydrocortisone (100 mg every 8 h) were continued for 24 hours postoperatively. Epinephrine initially was continued into the postoperative period but was stopped due to hypertension. The patient's airway was extubated 10 hours after the procedure without significant morbidity. Her postoperative course was complicated by new-onset atrial fibrillation with rapid ventricular response on postoperative day 1. Management of atrial fibrillation prolonged the patient's hospitalization, and she was discharged on postoperative day 7. Subsequent procedures to repair the descending aorta, a carotid-to-subclavian bypass and thoracic endovascular aortic aneurysm repair, were executed under strict normothermia without pretreatment. Techniques used to maintain normothermia included elevation of ambient operating room temperature, forced air warming, and the administration of warmed fluids. Neither procedure elicited an urticaric response.

Discussion

CIU is a syndrome characterized by the development of a wide array of symptoms including hives, angioedema, and shock.^{1–4} CIU has a variable presentation with a proposed classification system of type 1: localized urticaria; type 2:

systemic reaction such as generalized urticaria without hypotensive symptoms; and type 3: severe systemic reactions associated with hypotension.¹ The majority of patients (70.9%) experience improvement or resolution of symptoms with time.⁵ Diagnosis of CIU is made through careful patient history and a cold stimulation test. The cold stimulation test, also known as the "ice cube" test, involves the application of a cold stimulus between 0° to 4°C (often an ice cube) to the skin of the patient's volar forearm for either 5 or 7 minutes. The test is positive if the patient develops a reaction on skin rewarming.¹ Patients with a history of oropharyngeal swelling also are more likely to experience fulminant systemic reactions.² About 1 in 3 patients will experience systemic reactions and be classified as having type 3, with the majority of severe reactions associated with cold water immersion.² Intraoperative hypotension and facial edema after a cold intravenous stimulus have been reported.¹¹ Guidelines exist for the treatment of CIU, but they only address chronic approaches and do not include perioperative recommendations.¹² The mainstays of treatment are avoidance of triggers such as cold weather, cold surfaces, and cold foods/beverages combined with the administration of antihistamines.^{4,12}

The pathophysiology of CIU remains controversial, with the leading theory being the release of mast cell mediators such as histamine, prostaglandin D₂, leukotrienes, tumor necrosis factor alpha, eosinophilic chemotactic factor, and platelet activating factor.⁴ Recent research has implicated immunoglobulin E as a possible pathogenic factor.² A small percentage of cases are associated with cryoproteins such as cryoglobulin, cold agglutinin, and cryofibrinogen.² Important in the pathophysiology of CIU is the time course of the reaction after exposure to cold. Histamine levels peak 4-to-8 minutes after removal of the cold stimulus, and some patients may experience a decrease in systemic blood pressure.² The hypotension typically lasts between 10 and 45 minutes.¹³ Swelling and urticaria also occur on skin rewarming, which place patients with CIU at high risk for anaphylactic shock states during the rewarming phase of cardiopulmonary bypass.⁴

Cardiopulmonary bypass and circulatory arrest have been executed safely in patients with CIU. The following 2 approaches have been taken: to maintain strict normothermia more common with cardiopulmonary bypass or to institute a pretreatment regimen more common with circulatory arrest (Table 1). Common to all pretreatment regimens for hypothermia is the administration of histamine 1- and 2-receptor antagonists and corticosteroids. Fitzsimons et al³ and Ellis et al¹⁰ verified the efficacy of pretreatment followed by a cold stimulation test in the immediate preoperative period.

The treatment regimen developed for the patient described in this case report was tailored to her current symptomatology. It was different from that of previously reported cases because pretreatment was initiated on the day of surgery, a formal consultation with an allergist was not obtained, and low-dose epinephrine was administered. This patient had a history of type-2 CIU; however, she had experienced progressive improvement in her symptoms over time. On the day of surgery, she denied severe or systemic symptoms, which would have been more

Table 1
Summary of Treatment Regimens Used for Patients with Cold-Induced Urticaria Requiring Cardiac Bypass or Circulatory Arrest

Case Summary	Disease History	Preoperative Medications	Intraoperative Medications	Intraoperative Temperatures and Times	Rewarm Medications	Postoperative Medications	Citation
47-year-old man requiring CABG	6-year history of CIU with symptoms after eating ice cream or holding a cold drink	3 wk prior 20 mg prednisone daily PO 300 mg cimetidine 4 times daily PO 50 mg diphenhydramine 4 times daily PO Before going to OR 100 mg hydrocortisone IM	Before induction 300 mg cimetidine 90 mg diphenhydramine 100 mg hydrocortisone Before bypass 100 mg hydrocortisone	Core 31°C Cardioplegia 4°C	300 mg cimetidine 90 mg diphenhydramine*	None	Johnston 1982 ⁸
69-year-old man requiring aortic valve replacement and CABG	History of CIU with diffuse urticaria when exposed to cold water, tongue itching with cold foods, localized urticaria when handling cold objects	5 d prior 180 mg fexofenadine daily PO 150 mg ranitidine daily PO 12, 6, and 1 h prior 60 mg methylprednisolone 50 mg ranitidine 75 mg diphenhydramine	1 h before bypass 2 g methylprednisolone	Core 32°C Cardioplegia 4°C	30 min before rewarm 60 mg methylprednisolone 50 mg ranitidine 75 mg diphenhydramine	6 h postoperative 60 mg methylprednisolone 50 mg ranitidine 75 mg diphenhydramine	Lancey 2004 ⁹
34-year-old woman requiring mitral valve repair	8-year history of CIU with severe hives and lightheadedness after cold water exposure	6 h prior 50 mg diphenhydramine 50 mg ranitidine 60 mg methylprednisolone	At incision 50 mg diphenhydramine 50 mg ranitidine 60 mg methylprednisolone	Core 37°C Cardioplegia 20°C Cross-clamp time 74 min Bypass time 109 min	None	None	Irani 2007 ⁶
41-year-old woman requiring CABG	10-year history of CIU with symptoms after exposure to cold stimulus	12 h prior 1 mg/kg methylprednisolone	Before induction 1 mg/kg methylprednisolone 45 mg pheniramine	Core > 36°C Isothermic cardioplegia	None	0.5 mg/kg methylprednisolone daily tapered over 3 d	Bakay 2010 ⁴
67-year-old woman requiring CABG	History of CIU that responded well to antihistamine treatment	None	Before induction - hydrocortisone - ranitidine - chlorphenamine	Core 35.6°-37.3°C Isothermic cardioplegia	None	None	Booth 2011 ⁷
70-year-old man requiring CABG and ascending aortic aneurysm repair	History of CIU including earlier life-threatening reaction to cold with anaphylactic reaction to cold water immersion	7 d prior 20 mg cetirizine BID PO 150 mg ranitidine BID PO 10 mg montelukast daily PO 25 mg prednisone BID PO, 5 days prior - metoprolol replaced with amlodipine 1 h prior 2 g methylprednisolone 100 mg diphenhydramine 50 mg ranitidine	1 h before bypass 125 mg methylprednisolone 100 mg diphenhydramine	Core 28°C Total DHCA time 11 min Bypass time 159 min	60 mg methylprednisolone 100 mg diphenhydramine 50 mg ranitidine†	6 h postoperative 60 mg methylprednisolone 50 mg diphenhydramine 50 mg ranitidine	Ellis 2013 ¹⁰
57-year-old man requiring pulmonary thromboendarterectomy	25-year history of CIU with symptoms of urticaria, erythema, tachycardia, dizziness, and fatigue with exposure to cold water	13 and 6 h prior 50 mg diphenhydramine PO 150 mg ranitidine PO 1 h prior 50 mg diphenhydramine 100 mg ranitidine 100 mg hydrocortisone	At induction 250 mg methylprednisolone 100 mg ranitidine 50 mg diphenhydramine	Core 17°-21.6°C Total DHCA time 61 min Bypass time 232 min	25 mg diphenhydramine†	None	Fitzsimons 2015 ³

NOTE. All medications given intravenously unless otherwise specified.

Abbreviations: BID, twice daily; CABG, coronary artery bypass grafting; CIU, cold-induced urticaria; DHCA, deep hypothermic circulatory arrest; IM, intramuscularly; PO, orally.

*Increase in histamine after rewarming without clinical complications.

†Patient was hypotensive, necessitating inotropic and/or pressor support during rewarming.

consistent with a diagnosis of type-1 CIU. Prior patients with CIU presenting for DHCA or mild hypothermic cardiopulmonary bypass all received pretreatment varying in duration between 3 weeks and 6 hours before surgery. The patient in this case report received her first dose of prophylaxis 1 hour before the scheduled case start. The efficacy of her premedication regimen was verified with a 7-minute cold stimulation test before she was taken to the operating room.

Epinephrine, which is known to stabilize mast cell membranes and decrease release of mast cell mediators,¹⁴ was added to her intraoperative treatment regimen. Rewarming is the most likely time for a systemic reaction to occur due to the release of vasoactive substances from mast cells, so epinephrine was started before rewarming. This was a novel addition to other CIU treatment protocols found in the literature (see Table 1). Postoperatively, the patient became hypertensive without signs of a systemic reaction or the need for inotropic support so epinephrine was discontinued.

In summary, CIU is a rare syndrome affecting 0.05% of the population⁵ that can cause a wide range of symptoms from hives to cardiovascular collapse.¹ In this case report the authors discuss a same-day regimen and the addition of epinephrine infusion to the pretreatment of a patient with CIU requiring DHCA.

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