Cold agglutinins in patients undergoing cardiac surgery requiring cardiopulmonary bypass

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Objectives: Cold agglutinins (CA) are circulating autoantibodies present in most humans. They are active below normal body temperatures. Cold hemagglutinin disease involves the presence of CA sufficiently active at temperatures in the periphery to produce hemolysis or agglutination. Systemic hypothermia and cold cardioplegia may result in agglutination or hemolysis. We reviewed the experience of a large referral center in managing patients with CA and cold hemagglutinin disease undergoing cardiac surgery requiring cardiopulmonary bypass.

Methods: The electronic medical records from 2002 to 2010 were searched to identify patients with CA or cold hemagglutinin disease who underwent cardiac surgery requiring cardiopulmonary bypass. Information related to preoperative CA testing and treatment, surgery, cardiopulmonary bypass, postoperative complications, and mortality was recorded.

Results: Sixteen patients underwent 19 procedures requiring cardiopulmonary bypass. Six patients had cold hemagglutinin disease. The identification of CA was made intraoperatively in 3 patients. One patient underwent preoperative plasma exchange. Cold blood cardioplegia was used in 2 of 16 procedures using cardioplegia, with the remaining using warmer blood cardioplegia. The lowest recorded intraoperative core temperature was less than 34°C in 1 case. CA-related postoperative hemolysis requiring transfusion was present in 1 patient, which was resolved with active warming. No patient had evidence of permanent myocardial dysfunction, had a neurologic event, required dialysis, or died within 30 days.

Conclusions: All patients with CA/cold hemagglutinin disease at the Mayo Clinic College of Medicine safely underwent cardiac surgery without major adverse morbidity or mortality. Patients with CA but without evidence of cold hemagglutinin disease can safely undergo normothermic cardiopulmonary bypass at 37°C and warm cardioplegia without further testing. Patients with cold hemagglutinin disease should undergo laboratory testing including CA titers and thermal amplitude and hematology consultation before cardiac surgery. (J Thorac Cardiovasc Surg 2013;146:668-80)

Cold agglutinins (CA) are autoantibodies that become active at temperatures below physiologic body temperature. These antibodies are present in most humans but are rarely of clinical significance because they do not react at temperatures that are normally seen by the blood.[1] Cold hemagglutinin disease (CHAD) is characterized by the formation of CA that are sufficiently active at temperatures achieved in the peripheral circulation, such as the distal extremities on exposure to cold, allowing hemolysis or agglutination to occur.[2,3]

It is important to distinguish between CA and CHAD in that one represents a benign variant of normal and the other is a pathologic process. The benign and pathologic autoantibodies are directed toward the same common red blood cell antigens, most commonly IH, I, or i, but differ in that the benign autoantibodies are usually polyclonal, cause agglutination or complement fixation at less than 25°C, and have titers less than 64 at 4°C and less than 16 at 22°C. The antibodies in CHAD are usually monoclonal, cause agglutination or complement fixation at 30°C to 37°C, and have titers greater than 512 at 4°C and greater than 128 at 22°C.[1]

CHAD is responsible for 16% to 32% of all autoimmune hemolytic anemias in both children and adults, with an estimated prevalence of 10 to 16 cases per 1 million people.[3-5] With rare exception, CHAD almost exclusively involves immunoglobulin-M autoantibodies.[3,6] The CA present in CHAD bind to red blood cells at the colder temperature of the peripheral body (eg, hands, feet, ears, and nose), causing agglutination and complement fixation. Because of the cooler temperatures, complement cannot activate but remains on the red cell surface. On rewarming in the body's core, the CA release, but complement in the form of C3b remains on red blood cells. Extravascular hemolysis occurs predominantly in the liver as the complement-coated red blood cells are removed by macrophages.[2,7] The severity of CHAD varies greatly among patients according to antibody titer and thermal activity of the CA. Although CA do not

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Abbreviations and Acronyms
CA = cold agglutinins
CHAD = cold hemagglutinin disease
CPB = cardiopulmonary bypass
IABP = intra-aortic balloon pump

typically react at temperatures greater than 30°C, Rosse and Adams[8] report patients with CHAD antibodies active at normothermia (37°C). CHAD may be a primary disorder or be secondary to malignancy (most commonly lymphoma), infection (infectious mononucleosis or *Mycoplasma pneumonia* infection), or autoimmune diseases.[2-4]

Cardiac surgery requiring cardiopulmonary bypass (CPB) and hypothermia carries a significant risk of morbidity in patients with CA or CHAD. Systemic hypothermia and cold cardioplegia may result in blood reaching temperatures that can cause agglutination and hemolysis.[9,10] Hemolytic anemia[11] and myocardial dysfunction[12] have been attributed to CA in patients undergoing hypothermic CPB, whereas dysfunction of other end organs secondary to CA is a hypothetical concern.[3,9] Experience involving patients with CA and CHAD undergoing cardiac surgery requiring CPB consists of case reports and small series[9,12] of less than 20 cases that do not distinguish patients with CA from those with CHAD and case reports of patients with CA and CHAD. The purpose of this study was to review the recent experience of a single large tertiary referral center in managing patients with CA or CHAD undergoing cardiac surgery requiring CPB.

MATERIALS AND METHODS

This study was approved by the Mayo Foundation Institutional Review Board. A computer-generated search of the electronic medical records from 2002 to 2010 (the time period from the implementation of the electronic anesthesia record to the end of the searchable patient records at initiation of this study) was performed to identify patients aged 16 years or greater with a diagnosis of CA, CHAD, or related diagnoses, such as cold autoimmune hemolytic anemia, cold hemolysis, and paroxysmal cold hemoglobinuria, who had given permission for their medical record to be used for research. These patients were then cross-referenced for those who underwent surgery requiring CPB. Individual patient records were then reviewed by one of the authors (D.W.B.) to verify the presence of CA or CHAD and surgery requiring CPB.

A standardized data-collection form was used. Demographic information (age at time of surgery and gender) was recorded. The electronic medical records of each patient were reviewed for preoperative information related to the surgery (diagnosis and operation type) and CHAD or CA (method of diagnosis; timing of diagnosis in relation to surgery; presence of CHAD signs and symptoms, eg, anemia, hemolysis, acrocyanosis; cause of CHAD, eg, infections, lymphoproliferative disorder, or unknown; presence of paroxysmal cold hemoglobinuria; CA antibody titer; CA thermal amplitude; direct antiglobulin test; hemoglobin; creatinine; whether valvular pathology was thought to contribute to hemolysis as indicated in physician notes; dialysis dependency; ejection fraction from transthoracic echocardiogram; lactate dehydrogenase; haptoglobin; and whether a hematologist was consulted before surgery). Details of treatments of CHAD within 90 days of surgery were recorded (plasma exchange; medical therapies, including rituximab, cyclophosphamide, chlorambucil, and glucocorticoids; intravenous immunoglobulin; history of splenectomy; erythropoietin; and transfusions). Generalized anesthetic information consisting of American Society of Anesthesiologists physical status classification and emergency or scheduled nature of surgery was noted. The intraoperative anesthetic record, surgical note, and perfusionist's record were reviewed for documentation of warming methods used; duration of CPB; duration of aortic crossclamp; presence of circulatory arrest; cardioplegia techniques, including delivery method, temperature, composition, intervals, number of doses, and specific notations by the surgeon or perfusionist related to the cardioplegia; notations related to agglutination by the surgeon or perfusionist; nadir nasal and bladder temperatures; use of antifibrinolytics; and fluid and transfusion requirements. The postoperative record was reviewed for details of vasoactive medication or intra-aortic balloon pump (IABP) therapies as a marker of heart failure, transfusion requirements, aforementioned laboratory studies (including hemoglobin nadir and creatinine peak in the first 2 postoperative days), chest tube output in the first 48 postoperative hours, complications of transfusions as noted in the daily progress notes, and death within 30 days. Statistical analysis consisted of determination of mean ± standard deviation, median, and range for continuous variables and quantification (%) for categoric variables.

RESULTS

We identified 16 patients with CA or CHAD who underwent 19 cardiac procedures requiring CPB. Of these 16 patients, 6 had evidence of CHAD before surgery (Appendix Table 1). Of the 10 patients with CA, 6 had CA identified at the time of preoperative type and screen at the Mayo Clinic College of Medicine or during CPB. The mean age at the time of surgery was 69 ± 15 years (median, 73 years; range, 16-81 years), and 10 of 19 (53%) were male. Details related to the CA or CHAD and preoperative testing are shown in Appendix Table 1. No patient had a history of paroxysmal cold hemoglobinuria. None of the surgeries were performed on an emergency basis. All procedures involved patients with American Society of Anesthesiologists physical status classification 3 (74%) or 4 (26%).

Preoperative treatment of CHAD or treatments that could have affected CA levels or CHAD included plasma exchange in 1 patient, glucocorticoids in 1 patient, and a history of splenectomy in 1 patient. Patient 1 underwent preoperative plasma exchange. A single 1.0 volume plasma exchange was performed using the COBE Spectra version 7.0 software (TerumoBCT, Lakewood, Colo) with ACD-A containing 7000 units of heparin as the anticoagulant. Replacement was 5% normal serum albumin with 3 units of fresh-frozen plasma at the end of the procedure. The choice of fresh-frozen plasma as a replacement volume was made to replace coagulation factors before surgery. Patient 5 had received prednisone 20 mg orally daily for 5 days preceding surgery for bronchitis and not to treat the CA. Patient 14 had a history of hemolytic anemia with the presence of both warm and cold autoantibodies. A splenectomy was performed months before cardiac surgery, with improvement in hemolysis after this intervention. Patient 2 was transfusion dependent before both surgeries because of ongoing hemolysis from CHAD

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