Cold haemagglutination is a primary or acquired autoimmune disease involving antibodies that lead to agglutination of red blood cells at low temperature followed by complement fixation and haemolysis on rewarming. This disease can lead to adverse consequences in patients undergoing cardiothoracic surgery, especially when hypothermic cardiopulmonary bypass is applied. The authors discuss the management of two patients who underwent mitral valve replacement surgery while cold agglutinins were detected in the perioperative period. In the first patient, the diagnosis was made preoperatively followed by administration of glucocorticoids to achieve acceptable level of antibody titers. The second patient experienced haemoglobinuria during her intensive care unit stay. The case report describes the pathophysiology of cold agglutination, relevant laboratory investigations such as antibody titers and thermal amplitude, identification of at-risk patients, and management strategies to avoid serious complications.

**Key words:** Anaesthesia, cardiac surgery, cold agglutinins
was prescribed at a dose of 60 mg once daily for 1 month and CA titers were repeated periodically, as shown in Table 1. The patient was taken up for surgery after confirming CA titers of less than 1:16 at 30°C. He underwent uneventful balanced general endotracheal anaesthesia. Comprehensive haemodynamic monitoring included a radial arterial catheter, a central venous triple lumen catheter, and transoesophageal echocardiography (TOE). Intraoperatively, intensive temperature monitoring was done and all necessary precautions were taken to avoid exposure to the active temperature range of CAs. Intravenous fluids and irrigation fluids were warmed before administration. The inhalational gas supplied to the patient was set at 37°C using a heated circuit. Lower body thermal blanket and higher operation theatre temperature helped to maintain the core temperature above 34°C. The patient was anticoagulated with heparin to achieve activated clotting time (ACT) of more than 480 s. Warm crystalloid fluid was used to prime the CPB circuit and warm blood cardioplegia was delivered through aortic root to sustain electromechanical silence while targeting the myocardial temperature above 32°C. Pressures within the CPB and cardioplegic circuits remained within the normal limits throughout the procedure. The circuitry was visually monitored for any evidence of agglutination of the RBCs. A 27-mm size Medtronic mechanical mitral valve (MV) prosthesis was inserted after excising the native valve tissue. The total cross-clamp time was 66 min, and the patient was weaned successfully from CPB with minimal inotropic support of dobutamine. Inspection on TOE revealed normal biventricular systolic function and normal functioning of the implanted MV prosthesis. The patient underwent clinical fast tracking in the intensive care unit (ICU) with no evidence of haemolysis or end organ dysfunction. The patient was discharged on the seventh postoperative day.

Case 2
A 34-year-old female was operated for MVR in view of severe MS. After an uneventful surgery, she was shifted to the ICU with stable haemodynamics on dobutamine (5 μcg/kg/min). Her first hour mediastinal drain output was approximately 200 ml. Protamine (1 mg/kg) was administered after checking the ACT of 150 s. Noradrenaline (0.1 μcg/kg/min) was initiated and 200 ml of crystalloid was infused to maintain perfusion pressure and central venous pressure. Arterial blood gas analysis showed haemoglobin of 8 gm/dl. Therefore, 2 units of cross matched packed red blood cells were requested immediately and transfused rapidly to maintain systemic blood pressure. She experienced coca-colored urine after 1 h of blood transfusion. Her core temperature was recorded as 33°C. The transfused blood bag and urine sample was sent to haematology laboratory for transfusion reaction workup. The transfused blood was found to be compatible with the patient’s blood group and adequate cross matching was ensured. However, free haemoglobin in urine, increased LDH (494 IU/L), and indirect serum bilirubin levels of 3.2 mg/dL (normal serum bilirubin: 0.2–1.2 mg/dL with indirect component ranging 0–0.9 mg/dL) confirmed an event of intravascular haemolysis. The haematology team was actively involved. Polyspecific direct antiglobulin tests were found weakly positive, revealing cold autoantibodies [Table 2].

There was no prior history of cold agglutinins, hypercoagulability, anaemia, recent infection, malignancy, or chronic exposure to any drug. She was completely asymptomatic in the preoperative period. Her intraoperative course was also uneventful. The MV was replaced using normothermic CPB strategy as per our institutional protocol and her core temperature was maintained above 34°C. Postoperative TOE examined normal prosthetic valve structure and function ruling out possibility of any paravalvular leak. Haematuria occurred due to cold haemagglutination after 5 hours of surgery. The management included active warming of the patient using thermal blanket and instillation of warm saline through the nasogastric tube to obtain core temperature of 36°C. The warm cross-matched leukocyte-depleted blood was transfused using in-line warmer to maintain serum haemoglobin above

| Temperature   | Diagnosis | 14 days after Steroid Therapy | 21 days after Steroid Therapy | 28 days after Steroid Therapy |
|---------------|-----------|------------------------------|------------------------------|------------------------------|
| 4°C           | 1:1024    | 1:512                        | 1:512                        | 1:512                        |
| Room temp (22°C) | 1:512    | 1:256                        | 1:256                        | 1:128                        |
| 30°C          | 1:256     | 1:32                         | 1:16                         | 1:16                         |
| 37°C          | Trace     | Trace                        | Trace                        | -                            |

*CA – Cold agglutinins*
10 mg/dl. Subsequent laboratory testing revealed no evidence of intravascular haemolysis and the patient was shifted to the surgical ward. Both the patients were informed about the finding of CAs and were issued Medalert card.

**DISCUSSION**

CAs are present in most humans and are of rare clinical significance. They are of two types—benign antibodies get activated at temperatures below the physiologic body temperature. On the contrary, the pathological variant known as CHAD occur due to autoantibodies that get activated at cold temperatures in the peripheral circulation. The benign autoantibodies are usually polyclonal and cause haemagglutination and complement fixation at less than 25°C. The antibodies in CHAD are usually monoclonal and cause complement fixation at 30°C to 37°C, allowing agglutination and haemolysis.[1]

During general anesthesia, heat is lost in a number of ways; predominantly by surface cooling through radiation and convection mechanisms, accounting for up to 40% and 30% of heat loss, respectively.[2] In light of recognition of these factors, simple measures such as forced-air warming blankets are being increasingly utilised, especially in long duration vascular, plastic, and neurosurgeries to limit the heat loss. However, presence of CAs in surgeries involving deliberate hypothermia, such as cardiac surgery and renal transplantation, pose unique anaesthetic challenges. Individuals can develop haemolytic complications and even graft failure.

Activation of CAs during hypothermic CPB may result in massive haemagglutination, lysis, and microvascular thrombosis. This can manifest as intracoronary thrombosis, high pressures in the CPB circuit, incomplete cardioplegic delivery, and therefore, inferior myocardial protection.[3,4] Adverse clinical sequelae include cerebral or myocardial infarction and hepatic or renal failure.[3,5] Therefore, preoperative detection of CAs and subsequent implementation of all the necessary precautions is of paramount importance in cardiac surgery patients to avoid catastrophic consequences. There are few case reports in the literature describing specific intraoperative concerns in cardiac patients and management of CPB with modified cardioplegia delivery techniques.[1,6-7] In the present case report, the authors discuss two different case scenarios outlining the preoperative and postoperative management of patients detected with CHAD undergoing cardiac surgery.

Detection of agglutination during immediate spin antibody screening or during ABO typing, which occurs at room temperature, may signify pathological variant of CAs, as reported in our first patient. Patients may experience symptoms including acrocyanosis, fatigue, dyspnoea, haemoglobinuria, weakness, and weight loss. Further laboratory testing relevant to CHAD includes those related to haemolysis and others related to the quantification and activity of CA antibodies. The investigation panel includes direct antiglobulin test, LDH, haptoglobin level, free plasma haemoglobin, and serum indirect bilirubin. The CA antibody titer and thermal amplitude indicate the clinical severity of CHAD.[1,3] The CA titers are considered clinically significant when above 64. Thermal amplitude is the measure of the highest temperature at which agglutination is observed in vitro. During laboratory evaluation, specific temperatures are typically examined: 4°C, 22°C, 30°C, and 37°C, with a thermal amplitude of 30°C being regarded as clinically significant for disease activity in patients with positive CA titers of ≥ 1:64. Higher thermal amplitude represents autoantibody activity at warmer temperatures and thus having more potential of red blood cells haemolysis. Thermal amplitude determination is vital to determine the cut-off point of temperature that can be tolerated in a particular case. Some have recommended that all patients requiring CPB should undergo routine testing for CAs but others have questioned the utility and feasibility of this recommendation.[3] At our institute, we actively seek haematology consultation and follow rigorous testing for CA titer and thermal amplitude whenever there is a strong suspicion of CHAD. The haematologists serve as part of the multidisciplinary team approach in patient’s risk stratification, guiding and interpreting the preoperative testing, and assisting with preoperative reduction of CAs. Surgeons and perfusionists are consulted to plan the case-by-case management of CPB temperature and cardioplegia delivery keeping account of CA severity and thermal amplitude.
Preoperative medical therapies such as plasma exchange, rituximab, cyclophosphamide, chlorambucil, glucocorticoids, and intravenous immunoglobulin may be administered in patients with CHAD to reduce the autoantibody titers. Erythropoietin and red blood cell transfusions may help to treat anaemia in patients with active disease. Plasma exchange provides a rapid and reliable reduction in CA antibody titer temporarily and is often used for CHAD patients with active haemolysis. We consider reducing the antibody titer below 64 prior to the surgery and prefer the preoperative use of glucocorticoid. Our practice has been strict avoidance of hypothermia using forced-air warming device and warmed intravenous fluids in the operation theatre. Intraoperative management of patients with CAs focuses into strategies pertaining to CPB and cardioplegia. We employ normothermic CPB and administer warm blood cardioplegia to keep core temperature above the thermal amplitude. A close watch on CPB circuitry is always kept to rule out agglutination.

The second patient experienced high drainage from the mediastinal tube during her postoperative course in the ICU. The bleeding patient algorithm was followed. She developed haemoglobinuria 5 hours after the cardiac surgery following blood transfusion. Haematuria in early postoperative period has been associated with CPB, high haematocrit, prosthetic valve, mismatched blood transfusion, and iatrogenic trauma during urinary catheter insertion. It frequently begins in the operation theatre itself when it is secondary to CPB issues, high haematocrit, or paravalvular leak. A history of blood transfusion usually precedes a transfusion reaction. We accept the fact that the second patient developed hypothermia inadvertently in ICU. Rapid transfusion of cold blood led to reduction in her systemic temperature below the thermal amplitude of CAs leading to intravascular haemolysis. Active warming and correction of anaemia suffice in most cases, as the condition is self-limiting. The next step would have been plasma exchange in this case for rapid reduction of autoantibodies. An important point is to have a high index of suspicion and actively involve haematology team for accurate diagnosis and management.

**CONCLUSION**

This case report intends to bring clinical awareness of cold agglutinin disease among anesthesiologists. The multidisciplinary team approach is vital to deal with the disease during the perioperative period. Strict vigilance for agglutination, haemolysis, and end organ damage is required to avoid life-threatening events.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Barbara DW, Mauermann WJ, Neal JR, Abel MD, Schaff HV, Winters JL. Cold agglutinins in patients undergoing cardiac surgery requiring cardiopulmonary bypass. J Thorac Cardiovasc Surg 2013;146:668-80.
2. Young S, Haldane G. Major colorectal surgery in a patient with cold agglutinin disease. Anaesthesia 2006;61:593-6.
3. Patel PA, Ghadimi K, Coetzee E, Myburgh A, Swanevelder J, Gutsche JT. Incidental cold agglutinins in cardiac surgery – Intraoperative surprises and team-based problem-solving strategies during cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2017;31:1109-18.
4. Alizadeh K, Tabari M, Mottahedi B. Problems of cold agglutinins in cardiac surgery: How to manage cardiopulmonary bypass and myocardial protection. J Cardiothorac Med 2014;2:137-40.
5. Bracken CA, Gurkowski MA, Naples JJ. Cardiopulmonary bypass in two patients with previously undetected cold agglutinins. J Cardiothorac Vasc Anesth 1993;7:743-9.
6. Agarwal SK, Ghosh PK, Gupta D. Cardiac surgery and cold-reactive proteins. Ann Thorac Surg 1995;60:1143-50.
7. Gokhale AG, Suhasini T, Saraswati V, Chandrasekhar N, Rajagopal P. Cold agglutinins and warm heart surgery. J Thorac Cardiovasc Surg 1993;105:557.