

Normothermic Cardiac Surgery with Warm Blood Cardioplegia in Patient with Cold Agglutinins

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Cold agglutinins are predominately immunoglobulin M autoantibodies that react at cold temperatures with surface antigens on the red blood cell. This can lead to hemagglutination at low temperatures, followed by complement fixation and subsequent hemolysis on rewarming. Development of hemagglutination or hemolysis in patients with cold agglutinins is a risk of cardiac surgery under hypothermia. In addition, there is the potential for intracoronary hemagglutination with inadequate distribution of cardioplegic solutions, thrombosis, embolism, ischemia, or infarction. We report a patient with incidentally detected cold agglutinin who underwent normothermic cardiac surgery with warm blood cardioplegia.

Key words: 1. Cold agglutinins
2. Thoracic surgery
3. Cardiopulmonary bypass
4. Hemagglutination

CASE REPORT

A 66-year-old man presented to the emergency department with severe dyspnea and generalized edema. Six years previously, he had been diagnosed with moderate mitral regurgitation and tricuspid regurgitation. An electrocardiogram demonstrated inverted T waves, while a chest roentgenogram showed severe cardiomegaly, pulmonary edema, and right pleural effusion. An echocardiographic examination showed global biventricular hypokinesia (EF=40%), severe mitral regurgitation, and severe tricuspid regurgitation. His clinical data on admission were as follows: white blood cell count, 6,800/mm³; neutrophil segment (%), 83%; hemoglobin, 11.5 g/dL; hematocrit, 35.3%; platelet count, 49×10³/mm³; reticulocyte count (%), 2.5%; C-reactive protein, 6.7 mg/dL; er-

throcyte sedimentation rate, 68 mm/hr; total bilirubin, 2.7 mg/dL; alanine transaminase, 167 IU/L; and prothrombin time (international normalized ratio, INR), 2.67 INR. Routine preoperative antibody screening for cross-matching revealed an elevated cold agglutinin titer at 4°C (1:128). The patient gave no history of anemia or prior blood transfusion and had never consulted a hematologist. Because of severe symptoms of heart failure and progression of systemic organ dysfunction, an early operation was planned. Precautions were taken intraoperatively to avoid exposure to agents within the active temperature range for cold agglutination. The esophageal core temperature was maintained above 35°C and normothermic cardiopulmonary bypass (CPB) was initiated. The aortic cross clamp was applied and antegrade warm blood cardioplegia (with a high potassium concentration of 90 mEq/L) was de-

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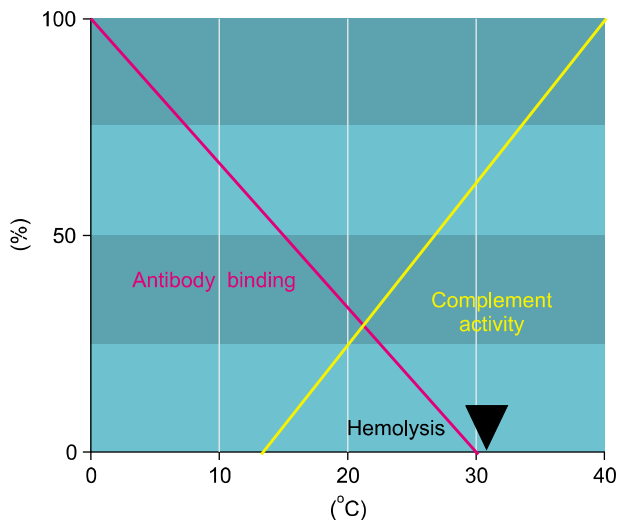


Fig. 1. Thermal amplitude: the temperature below which the antibodies become activated. ▼: thermal amplitude.

livered at the temperature of 35°C. Throughout the procedure, low-potassium (K^+ ; 30 mEq/L) warm blood cardioplegia was intermittently delivered within 20 minutes. There was no myocardial electrical activity necessitating an additional bolus of high-potassium cardioplegic solution. An isolated cleft in the anterior leaflet of the mitral valve and secondary tricuspid regurgitation were successfully repaired. The total cross-clamp time was 115 minutes, and the patient was weaned successfully from CPB. The patient had an uneventful postoperative course with regard to hemodynamic performance. He was discharged 59 days after surgery because of postoperative mediastinitis and was followed up at an outpatient clinic for 20 months.

DISCUSSION

Cold agglutinin disease (cold antibody disease) is caused by autoantibodies that react at decreased blood temperature and produce agglutination or hemolysis of red blood cells [1-3]. The causes of this situation include infections (especially mycoplasmal pneumonias or infectious mononucleosis), lymphoproliferative disorders, and idiopathic diseases (about half of cases). Infections tend to cause acute disease, whereas idiopathic disease (the common form in older adults) tends to be chronic [1]. The most clinically relevant characteristic of

cold agglutinins is thermal amplitude, the temperature below which the antibodies become activated (Fig. 1). If the screening for cold agglutinins is positive at 4°C, the thermal amplitude should be determined, and the titer determined for each temperature at which the screen is positive [1]. When the blood temperature drops below this threshold, cold agglutinins bind to erythrocytes, causing agglutination and binding of complement C1 complex. In turn, C1 esterase activates C4 and C2, generating C3 convertase which binds and splits C3, causing deposition of C3b on the erythrocytes [4]. Upon subsequent warming, immunoglobulin M is removed from the cell surface, and the agglutinated cells get detached from each other, while C3b remains bound on the cell surface. C3b activates C5, forming the membrane attack complex. This results in intravascular cell lysis. The majority of the C3b-coated erythrocytes are destroyed by reticulo-endothelial cells in the liver by C3b receptor-mediated phagocytosis, which is extravascular [4] (Fig. 2).

Cold agglutinin disease is of clinical importance for patients undergoing cardiac surgery procedures with hypothermic CPB and cold cardioplegia, or in other instances of therapeutic hypothermia [1,3,5]. Higher cold agglutinin titers and higher thermal amplitude are more clinically significant than low titers and low thermal amplitude. Indeed, several researchers have stated that patients with low-titer, low thermal amplitude antibodies may undergo operation without any change in the routine management plan [6]. During a cardiac operation, the cardioplegia solution at very low temperature is infused via coronary artery for myocardial protection. Thus, the titers of cold agglutinins at 4°C are probably the best guide to possible complications during cardiac surgery with cold blood cardioplegia. There are no widely accepted definitions of high and low titers; however, Lee et al. [7] suggested that titers less than 1:32 are low, and those greater than 1:128 are high. Holman et al. [2] reported a patient who developed intracoronary agglutination of the blood cardioplegia solution during coronary artery bypass surgery. The cold agglutinin had an agglutination titer of 256 at 4°C. During surgery, the heart was arrested using a 4°C blood cardioplegia solution, and agglutinated blood was found when the coronary artery was incised [2].

Treatment for patients with cold agglutinins during cardiac

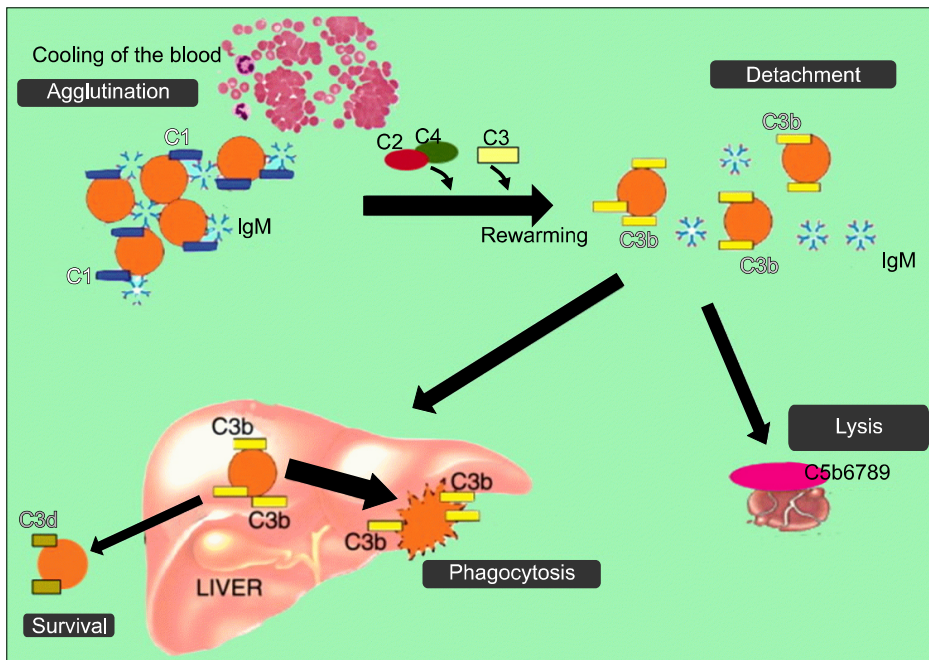


Fig. 2. The mechanisms of red blood cell agglutination and subsequent destruction in cold agglutinin disease. IgM, immunoglobulin M.

surgery using CPB is based on the etiology and severity of the problem. In cases of cold agglutinins caused by acute infection, elective surgery should be postponed for several weeks until the antibody disappears. If the urgency of surgery precludes this approach, the most sensible alternative is to use either normothermia or mild hypothermia using blood temperatures continuously maintained above the thermal amplitude to avoid the active temperature range of agglutination [3,5]. Hence, the presence of cold agglutinins with a high titer may represent a reasonable indication for the use of warm cardioplegia myocardial protection techniques while maintaining normothermic systemic temperatures. The benefits and risks of ‘warm heart surgery’ remain controversial and uncertain. However, several studies have suggested that it may be as safe as hypothermic cardiac surgery with regard to concerns such as myocardial preservation and the protection of other organs, such as the brain and the kidneys [8].

To conclude, we report a patient with incidentally detected cold agglutinins with a relatively high titer who underwent normothermic cardiac surgery with warm blood cardioplegia. Cold agglutininemia in patients requiring cardiac procedures using CPB can cause severe complications due to hemagglutination and hemolysis. In these patients, the use of warm blood cardioplegia combined with normothermic extracor-

poral circulation may have a successful outcome without complications of cold agglutinin after cardiac surgery.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Bratkovic K, Fahy C. *Anesthesia for off-pump coronary artery surgery in a patient with cold agglutinin disease.* J Cardiothorac Vasc Anesth 2008;22:449-52.
2. Holman WL, Smith SH, Edwards R, Huang ST. *Agglutination of blood cardioplegia by cold-reacting autoantibodies.* Ann Thorac Surg 1991;51:833-5.
3. Kansaku R, Kuwaki K, Amano A, et al. *Aortic valve replacement to a patient with high titer of cold agglutinin.* Ann Thorac Cardiovasc Surg 2012;18:259-61.
4. Stone MJ. *Heating up cold agglutinins.* Blood 2010;116:3119-20.
5. Aoki A, Kay GL, Zubiato P, Ruggio J, Kay JH. *Cardiac operation without hypothermia for the patient with cold agglutinin.* Chest 1993;104:1627-9.
6. Moore RA, Geller EA, Mathews ES, Botros SB, Jose AB, Clark DL. *The effect of hypothermic cardiopulmonary bypass on patients with low-titer, nonspecific cold agglutinins.* Ann

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Thorac Surg 1984;37:233-8.

7. Lee MC, Chang CH, Hsieh MJ. *Use of a total wash-out method in an open heart operation.* Ann Thorac Surg 1989; 47:57-8.

8. Ho KM, Tan JA. *Benefits and risks of maintaining normothermia during cardiopulmonary bypass in adult cardiac surgery: a systematic review.* Cardiovasc Ther 2011;29:260-79.