

## Problems of Cold Agglutinins in Cardiac Surgery: How to Manage Cardiopulmonary Bypass and Myocardial Protection

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### ABSTRACT

Cold agglutinins are of unique relevance in cardiac surgery because of the use of hypothermic cardiopulmonary bypass (CPB). Cold autoimmune diseases are defined by the presence of abnormal circulating proteins (usually IgM or IgA antibodies) that agglutinate in response to a decrease in body temperature. These disorders include cryoglobulinemia and cold hemagglutinin disease. Immunoglobulin M autoantibodies to red blood cells, which activate at varying levels of hypothermia, can cause catastrophic hemagglutination, microvascular thrombosis, or hemolysis. Management of anesthesia in these patients includes strict maintenance of normothermia. Patients scheduled for the surgery requiring cardiopulmonary bypass present significant challenges. Use of systemic hypothermia may be contraindicated, and cold cardioplegia solutions may precipitate intracoronary hemagglutination with consequent thrombosis, ischemia, or infarction. Management of CPB and myocardial protection requires individualized planning. We describe a case of MV repair and CABG in a patient with high titer cold agglutinins and high thermal amplitude for antibody activation. Normothermic CPB and continuous warm blood cardioplegia were successfully used.

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### Introduction

Cold agglutinins (CAs) are particular cold-reactive antibodies that react with the red blood cells (RBCs) when the blood temperature drops below normal body temperature causing increased blood viscosity and red blood cell clumping. Most individuals with cold agglutinins are not aware of their presence, as these antibodies have little impact on daily living, often necessitating no treatment. However, when those with cold agglutinins are exposed to hypothermic situations or

undergo procedures such as cardiopulmonary bypass with hypothermia during cardiac surgery, lethal complications of hemolysis, microvascular occlusion and organ failure may occur (1). (CAs) are cold-reactive antibodies, usually of the immunoglobulin M subtype, that cause (RBCs) to agglutinate at low temperatures (2). At low temperatures occur hemagglutination, followed by complement fixation and subsequent hemolysis is the again warm (2, 3). This autoimmune phenomenon is of unique relevance during

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cardiac operations when hypothermic cardiopulmonary bypass (CPB) and cardioplegia are instituted (4).

At normothermia, CA rarely has clinical significance; however, activation of CAs during CPB can lead to massive hemagglutination, hemolysis, and microvascular thrombosis. This can manifest intraoperatively as intracoronary thrombosis, incomplete cardioplegic delivery, or high pressures in the CPB circuit. Clinical sequelae can include cerebral or myocardial infarction, hepatic or renal failure, and hemolysis (3,5).

The importance of CAs depends on two factors: the plasma titer of CAs and the thermal amplitude at which hemagglutination occurs. Low levels of CAs can be found in the sera of healthy individuals (about 1:16), however at higher titers, CA activation is more likely. In addition, thermal amplitude, or the temperature below which antibody activation occurs, should be quantified preoperatively, then the temperature range should be maintained during the operation be warned to the surgeon. In this case report we aimed to describe a patient undergoing MV repair and CABG who had high titer CAs with high thermal amplitude. A brief literature review with the aim of management strategies is also undertaken.

## Case Report

A 73-year-old man presented with severe MR and severe 3VD. An angiogram revealed low left ventricular (LV) systolic function, with severe mitral regurgitation.

The patient had probably asymptomatic CAs due to a chronic Infectious Mononucleosis because IgG anti IM antibody was detected in laboratory studies. Preoperative testing demonstrated an elevated CA titer (1:512) with unusually high thermal amplitude of 32°C.

Precautions were taken intraoperatively to avoid exposure to agents within the active temperature range for cold agglutination. Anesthetic agents and fluids were warmed, including priming fluid for CPB. The operating room temperature was elevated, and a lower body-warming blanket was applied. The patient was anticoagulated with heparin to an activated clotting time (ACT) of 500 seconds.

Warm CPB was initiated, and the esophageal core temperature was maintained above 35°C. The aortic cross clamp was applied, and induction cardioplegia was given antegrade into the aortic root at a temperature of 35°C.

Throughout the remainder of the procedure, warm antegrade cardioplegia was given, every 15 minutes and electromechanical silence was sustained. Pressures within the CPB and cardioplegic circuits remained within normal limits. The

circuitry was visually monitored for evidence of agglutination of the RBCs.

Total revascularization was done and MV repaired with posterior anuloplasty. Total cross-clamp time was 96 minutes, and the patient weaned successfully from CPB and required minimal support with inotropes. Once separated from CPB, the circuit cooled to room temperature, and RBC agglutination could be seen within cardioplegic lines.

The patient's postoperative course was without evidence of hemolysis or end-organ dysfunction. The patient was discharged on the seventh postoperative day.

## Discussion

CAs are predominantly immunoglobulin M antibodies directed against the RBC I or i antigen. The clinical importance of CAs largely depends on their titer and thermal threshold, the highest temperature at which the antibody is active (6). As this is usually lower than ambient temperatures, CAs are usually of little clinical importance, with diagnosed CA disease having an approximate incidence of 1:75,000. However, in the situation of cardiac surgery, CAs might be of greater clinical importance due to the use of hypothermia for myocardial protection (2).

For the first time in 1980, Klein and colleagues (7) investigated cold agglutinin in relation to cardiac surgery. Most authors had noted these antibodies in routine preoperative testing, whereas a few were surprised by unexpected finding of agglutination in the CPB or cardioplegia circuit during operation or persistent hemolysis after operation (3). Moore and co-workers (8) were the first group to use routine preoperative clinical testing with the Ehrlich finger test and palm ice cube test. Most reports with preoperative detection of antibodies also thermal amplitude and standard the titer. For myocardial protection the most common technique in the past has been crystalloid/blood cardioplegia at higher temperature (9).

Hypothermic circulatory arrest technique depends on noncoronary collaterals for myocardial protection and may be insufficient. Hypothermic ventricular fibrillation or intermittent cross-clamping with or without fibrillation is useful only for coronary artery operations. The warm crystalloid washout technique is theoretically appealing but requires isolation of the heart from the remaining circulation, which may not be achieved due to noncoronary collaterals. The recently introduced technique of normothermic operation with warm blood cardioplegia delivered antegradely or retrogradely (3) obviates the need for hypothermia and prevents activation of these proteins while at the same

time providing excellent myocardial protection, which may be better than any other technique of myocardial management in these patients. We recommend warm heart operation as the preferred method.

The technique is described as providing myocardial protection with cold cardioplegia in a patient with cold autoagglutinins. The operation was done in normothermia and the coronary system was perfused with a normothermic (+37 degrees C) NaCl 0.9% solution to remove the blood before using the cold (+4 degrees C) cardioplegic solution. With this technique, the patient underwent an uneventful operation to relieve right ventricular-outflow stenosis operation (10). Recently, a new technique has been reported by Aoki and coworkers for myocardial protection that does not rely on hypothermia. In this method, the heart is continuously perfused with normothermic hyperkalemic blood cardioplegia during the cross-clamp period. Cardiac arrest is achieved and maintained using high levels of potassium. Hypothermia is not a part of this technique; so the danger of hypothermia can be avoided in the patient with cold agglutinin disease without compromising myocardial protection (11).

Myocardial preservation Techniques included: 1) cold crystalloid cardioplegia, 2) plasma exchange, 3) normothermic ischemic arrest, 4) warm crystalloid cardioplegia washout followed by cold cardioplegia, and 5) warm blood-potassium cardioplegia. None of the five techniques that are used is clearly superior to one another in order to avoid problems during open-heart surgery in patients with cold autoimmune disease. Hemolysis occurs in all patients during cardiopulmonary bypass, especially during rewarming. There was no protection from agglutination afforded by heparin, nor by hemodilution that has been reported by James Park coworkers (12).

Ko and Isom found that use of hypothermia during cardiopulmonary bypass and cardioplegia poses a special problem in patients with cold-reactive hemagglutination. They reported successful aortic valve replacement on a patient with severe aortic valve stenosis and severely symptomatic cold agglutinin induced hemolytic anemia. This case illustrates the various problems in the perioperative management of these patients (13). Berreklouw *et al* have reported previously that a technique is defined for providing myocardial protection with cold potassium crystalloid cardioplegia in a patient with cold autoagglutinins and hemolysins. The patient was just mildly cooled systemically (14).

## Conclusion

In conclusion, patients displaying high titer and high thermal amplitude CAs, need personal planning before cardiac operations, including consultation with a hematologist. Careful temperature monitoring must be undertaken intraoperatively to avoid CA activation causing catastrophic hemagglutination and hemolysis. We launched a safe technique with a successful outcome using normothermic CPB and continuous warm blood cardioplegia.

## Conflict of Interest

The authors declare no conflict of interest.

## References

1. Findlater RR, Schnell-Hoehn KN. When blood runs cold: cold agglutinins and cardiac surgery. *Can J Cardiovasc Nurs.* 2011; 21:30-4.
2. 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; 13: S0022-5223.
3. Hoffman JW Jr, Gilbert TB, Hyder M. Cold agglutinins complicating repair of aortic dissection using cardiopulmonary bypass and hypothermic circulatory arrest: case report and review. *Perfusion.* 2002; 17:391-4.
4. Atkinson VP, Soeding P, Horne G, Tatoulis J. Cold Agglutinins in Cardiac Surgery: Management of Myocardial Protection and Cardiopulmonary Bypass. *Ann Thorac Surg.* 2008; 85:310-1.
5. Itagaki T, Kikura M, Ishida C, Katoh H, Oikawa F, Iwamoto T, et al. Perioperative management for cardiovascular operations in two patients with cold agglutinin disease. *Masui.* 2008; 57:869-73.
6. Oshima M, Maeda H, Morimoto K, Doi M, Kuwabara M. Low-titer cold agglutinin disease with systemic sclerosis. *Intern Med.* 2004; 43:139-42.
7. Klein HG, Faltz LL, McIntosh CL, Appelbaum FR, Deisseroth AB, Holland PV. Surgical hypothermia in a patient with a cold agglutinin: management by plasma exchange. *Transfusion.* 1980; 20:354-7.
8. 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 Thorac Surg.* 1984; 37:233-8.
9. Landymore R, Isore OW, Barlam B. Management of patients with cold agglutinins who require open heart surgery. *Can J Surg.* 1983; 26:79-80.
10. Cerasuolo F, Vosa C, Arciprete P, Calvanese A, Barbagallo A. Cold agglutinins in a cardiosurgical patient: a successfully operated case. *G Ital Cardiol.* 1983; 13:122-4.
11. 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.
12. Park JV, Weiss CI. Cardiopulmonary Bypass and Myocardial Protection: Management Problems in

- Cardiac Surgical Patients with Cold Autoimmune Disease. *Anesth analg.* 1988; 67:75-8.
13. Ko W, Isom OW. Cardiopulmonary bypass procedures in patients with cold-reactive emagglutination. A case report and a literature review. *J Cardiovasc Surg (Torino)*. 1996; 37:623-6.
  14. Berreklouw E, Moulijn AC, Pegels JG, Meijne NG. Autoagglutinins and Hemolysins Myocardial Protection with Cold Cardioplegia in a Patient with Cold. *Ann Thorac Surg*. 1982; 33:521-2.