*Case Reports*

# Use of an Intravascular Warming Catheter

## during Off-Pump Coronary Artery Bypass Surgery in a Patient with Severe Cold Hemagglutinin Disease

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*Cold hemagglutinin disease with broad thermal amplitude and high titers presents challenges in treating cardiac-surgery patients. Careful planning is needed to prevent the activation of cold agglutinins and the agglutination of red blood cells as the patient's temperature drops during surgery.*

*We describe our approach to mitigating cold agglutinin formation in a 77-year-old man with severe cold hemagglutinin disease who underwent off-pump coronary artery bypass surgery without the use of preoperative plasmapheresis. This experience shows that the use of an intravascular warming catheter can maintain normothermia and prevent the activation and subsequent formation of cold agglutinins.*

*To our knowledge, this is the first reported use of this technique in a patient with cold hemagglutinin disease. The chief feature in this approach is the use of optimal thermal maintenance—rather than the more usual decrease in cold-agglutinin content by means of therapeutic plasma exchange.* ***(Tex Heart Inst J 2016;43(4):363-6)***

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Cold hemagglutinin disease (CHAD) is a type of autoimmune hemolytic anemia that results in the harmful presence of cold autoantibodies against red blood cells (RBCs). The cold agglutinins (CAs) found in patients with CHAD have a broad thermal amplitude that enables them to activate in exposed parts of the body, such as the peripheral circulatory system. The disease can be especially troublesome—to the point of causing serious morbidity—in patients who undergo perioperative hypothermia. In this case study, we report the novel use of an intravascular warming device to maintain normothermia and prevent RBC agglutination during off-pump coronary artery bypass (OPCAB) surgery.

## Case Report

In June 2011, a 77-year-old man with long-standing hypertension was evaluated for dyspnea on exertion, of 6 months' duration. Results from prior studies, including a sleep study, computed tomographic scan, and ultrasonography, were all noncontributory. The results of a nuclear stress test were normal, but coronary angiography revealed non-stentable coronary artery disease in the left anterior descending coronary artery (LAD). The patient was then referred to our institution for possible coronary artery bypass grafting.

The patient's medical history included, at the age of 63 years, hemolysis and chronic anemia that had led to a diagnosis of CHAD. In the past, he had experienced—after exposure to cold—black discoloration of his fingertips, toes, nose, and ears, which symptoms had been followed by dark urine and jaundice. As a result, he took special precautions to dress warmly and avoided going outside during winter months. In addition, hemolysis in association with a previous prostatectomy had necessitated 2 RBC transfusions.

The patient's laboratory values on admission to our institution were as follows: hemoglobin, 9.8 g/dL; reticulocyte count, 4.3% (normal range, 0.5%–1.5%); total bilirubin, 1.4 mg/dL (normal range, 0.3–1.1 mg/dL); direct bilirubin, 0.4 mg/dL (normal range, 0.1–0.4 mg/dL); lactate dehydrogenase, 382 U/L (normal range, 107–206 U/L); and haptoglobin, <8 mg/dL (normal range, 14–258 mg/dL).

In his initial blood-bank examination, antibody screening by gel methodology was negative. However, a direct antiglobulin test (DAT) was scored as 4+ agglutination for

**TABLE I.** Short Cold Panel

| Variable | **RT** (15 min) | **4 °C** (15 min) | **28 °C** (1 hr) | **32 °C** (1 hr) | **34 °C** (1 hr) |
|---|---|---|---|---|---|
| $R_1R_1$ | 4+ | 4+ | 2+ | 2+ | Weak + |
| Autocontrol | 0 | 3+ | — | — | — |
| Cord | 4+ | 4+ | — | — | — |

$R_1R_1$ = genotype representing red blood cells with haplotype DCe; RT = room temperature

C3d and as negative for immunoglobulin G (IgG) coating. Cold agglutinins were evaluated by determining the titers, and a thermal amplitude test was performed at 28, 32, and 34 °C. These temperature points were selected for testing because they are the most frequently used threshold temperatures during cardiopulmonary bypass (CPB) at our institution. The CA titers were strongly positive with a value of 1:16,384, and the thermal amplitude was 34 °C (Tables I and II).

On the basis of these results, the surgeon chose to use OPCAB to decrease hypothermic risk. To avoid the potentially harmful effects of CA activation by the mild hypothermia that often occurs during OPCAB, the surgical team paid careful attention to the maintenance of normothermia. This was particularly important in consideration of the hemolysis that had occurred after a minor temperature drop during the patient's previous prostatectomy (a fairly routine surgery). On the basis of discussions in multidisciplinary rounds, it was decided that an intravascular warming catheter would be used to regulate temperature intraoperatively. The Thermogard® XP system (Zoll Medical Corporation, an Asahi Kasei Group company; San Jose, Calif) is approved by the U.S. Food and Drug Administration for use in cardiac surgery patients, to reach or maintain normothermia during surgery and recovery; it is also approved for use in neurosurgery patients who need reversal of mild hypothermia.

The system comprises a multiballoon heat-exchanger, a catheter that is typically inserted through the common femoral vein into the inferior vena cava. Warmed saline solution is circulated through the catheter into the balloons in a closed-loop fashion; heat exchange occurs as the patient's venous blood passes over the balloons. The computer connected to the catheter remotely senses changes in the patient's core temperature and automatically adjusts it. This directly affects the core temperature without the need for a direct saline-solution infusion.

At the beginning of the operation, the intravascular warming catheter was inserted into the patient's right common femoral vein, left to rest in the inferior vena cava, and set at 37 °C. Other precautions were taken to ensure that normothermia was maintained, such as the use of warming intravenous fluids, warming blankets, and a warmer room temperature. The prominence and visibility of the LAD made OPCAB a suitable approach. The procedure progressed without complications. The patient's estimated blood loss was 500 mL. A 150-mL cell-saver (in total) was given intraoperatively, but no transfusions were necessary. The nadir body temperature during the entire procedure was 36.4 °C.

**TABLE II.** Other Serologic Testing

| Test | Result |
|---|---|
| Antibody screen | Negative |
| DAT IgG | 0 |
| DAT C3d | 4+ |
| Cold titers | 1:16,384 |

C3d = complement 3d; DAT = direct antiglobulin test; IgG = immunoglobulin G

The patient's immediate postoperative hemoglobin level was 8.9 g/dL. The chest tube output was minimal, at 120 mL in the first hour and 10 mL in the 2nd hour. However, 3 hours later, the hemoglobin had dropped to 6.7 g/dL, and 2 units of RBCs were transfused through the warmer. This transfusion resulted in a disproportionate increase of the patient's hemoglobin level to 11.4 g/dL, which led us to believe that the earlier hemoglobin measurement had been spuriously low. On postoperative day 1, we discontinued use of the Thermogard system.

Results of a bone marrow biopsy performed after surgery showed nodules that were positive for CD5 and CD20 antigens and negative for CD23 antigen and cyclin D1, thereby supporting a diagnosis of low-grade B-cell lymphoma that involved 5% of marrow cellularity. Serum protein electrophoresis revealed an immunoglobulin M (IgM) kappa monoclonal band.

## Discussion

The incidence of CAs in patients undergoing cardiac surgery is difficult to estimate, but it has been reported to be less than 1%.[1,2] Cold agglutinins are rarely of clinical significance because they tend to agglutinate RBCs at 0 to 4 °C, and they are usually polyclonal IgM anti-

bodies that occur in titers of less than 1:64.[3] In contrast, CHAD antibodies are often monoclonal and are found in titers of greater than 1:512.[3] The pathogenicity of CAs depends on both the titer and the thermal amplitude—the highest temperature at which agglutination is observed in vitro.[4] If the thermal amplitude of CAs exceeds 28 °C, they can bind to RBCs in the acral circulation (in the feet, hands, and nose, for example) and cause complement fixation. As the RBCs circulate back to warmer parts of the body, the IgM antibody dissociates but the C3b remains bound, eventually leading to extravascular destruction of the RBCs by the reticuloendothelial system, mainly in the liver.[5]

Cold hemagglutinin disease is a particular concern in patients undergoing therapeutic interventions that involve hypothermic conditions such as CPB. Potential complications include hemolytic anemia, microvascular occlusion, decreased organ perfusion, and renal failure.[6-8] Although there is extensive literature on the management of CAs (both benign and malignant) during CPB, relatively few reports highlight the consequences of CHAD in off-pump cardiac surgery.[2,7,9-11] The dangers of hypothermia are present even in off-pump procedures, because of radiant heat loss from sternotomy in a cold operating environment. Moreover, general anesthesia impairs thermoregulation, and regional anesthesia causes vasodilation, which results in additional heat loss.[10] Therefore, the risk of activating CAs during OPCAB remains substantial, especially when a patient has markedly elevated titers and a high thermal amplitude of CAs.

The management of CHAD in patients undergoing cardiac surgery requires careful multidisciplinary planning and coordination. No specific treatment is available, but proactive measures must be taken to prevent intraoperative RBC agglutination. Consideration should be given to the clinically significant temperatures encountered during cardiac surgery. For example, at our institution, patients' temperatures often decline to 34 °C during major cardiac off-pump surgery, despite standard warming measures, and frequently reach 28 °C during CPB cases. Because the thermal amplitude in this patient was 34 °C, we used an intravascular warming catheter that was preset to keep the patient's temperature at 37 °C. The lowest actual core temperature reached during surgery was 36.4 °C; thus, there was never an opportunity for agglutination of RBCs to occur, if one discounts our patient's ongoing acral exposure. The additional precautions that we used in this case (for example, warming blankets and a warmer room temperature) might not have been necessary because the intravascular warming catheter was able to maintain core temperature so well.

To our knowledge, the management of CHAD during OPCAB has been discussed in only 2 other case reports. In one report,[12] routine preoperative antibody screening and crossmatching revealed CAs in a 56-year-old woman. The titers were not reported, but the thermal amplitude was 30 °C, indicating a milder disease process. The operation was successfully completed with the use of a forced-air warming device (FAWD), a heating blanket to maintain the patient's temperature between 36 and 36.5 °C, and warm intravenous fluids. In contrast, in the 2nd report, an 82-year-old woman with CHAD, who underwent OPCAB, had a thermal amplitude of 34 °C with a high titer at room temperature of >1/30,000.[10] The severity of CHAD in this patient was similar to that in ours: she needed 2 cycles of preoperative plasmapheresis, the application of FAWDs to the lower body and the head, and the use of warmed intravenous liquids. The strategy of performing therapeutic plasma exchange (TPE) before surgery to reduce the CA titer is highly effective in removing IgM, which is 95% intravascular.[13,14] However, performing TPE can be technically difficult because of the challenge of maintaining the optimal temperature in the circuit. In addition, there are well-known risks associated with TPE, including abnormal hemostasis, significant volume shifts, and transfusion reactions if fresh-frozen plasma is used. Furthermore, we have seen agglutination within the TPE circuit at our institution in patients with CAs of high titer and high thermal amplitudes.

In conclusion, this to our knowledge is the first reported case of the use of an intravascular warming catheter to prevent agglutination during OPCAB in a patient with CHAD. The key feature in the success of our approach is the use of optimal thermal maintenance rather than the more usual decrease in CA content by TPE.

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