

CARDIAC SURGERY AND COLD AUTOANTIBODIES

Development of hemolysis in patients with cold agglutinins of high thermal amplitude or exacerbation of the rate of hemolysis in patients with cold agglutinin syndrome (CAS) are risks 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 (1-4). When measures have been taken to avoid the hematologic and cardiac consequences of cold exposure in patients with cold agglutinins, the reported results have been excellent (5).

Adverse Events.

Although complications are not common, there are some well-documented events precipitated during surgery by cold in patients with cold agglutinins of high thermal amplitude. Bedrosian and Simel (6) reported a patient with well-compensated chronic CAS who had an acute "life-threatening" hemolytic crisis during an elective herniorrhaphy in a cool (20°C) operating room. The patient's hematocrit decreased from 36% to a low of 12.6%. The cold agglutinin was an anti-I with a titer of 51,200 against adult (I) RBC at 4°C in albumin, and a titer of 100 at 30°C.

Wertlake et al (7) attributed hemolysis, which began during cardiac surgery under hypothermia, to an anti-HI cold agglutinin that destroyed A₂B donor RBCs in an A₁B patient. Preoperatively the hematocrit was 45 percent and it dropped progressively to a level of 30 percent on the fifth post-operative day and did not begin to rise until day 15 despite a reticulocytosis. However, the cause of the hemolysis is somewhat uncertain because the direct Coombs test was consistently negative, and the thermal amplitude of the antibody was elevated only transiently to a level of 22°C on postoperatively day 6.

Izzat et al (4) reported a case in which agglutination of RBCs occurred within 1 minute of initiation of antegrade cold blood cardioplegia at 10°C and led to embolization in the coronary microcirculation. After the multiple agglutinates were noted, a coronary sinus cannula was inserted through the right atrium and continuous retrograde cold crystalloid cardioplegia was infused. Agglutinates were noted to flush back from the coronary arteries into the aortic root. Nevertheless, the patient did not show any signs of cardiac damage postoperatively.

Diaz et al (8) observed large RBC agglutinates within the coronary vessels and the coronary sinus when a patient's rectal temperature decreased to 30°C from 36°C with cardiopulmonary bypass. This led to the diagnosis of previously unsuspected CAS. They stated that the most important principle in the immediate management of unanticipated cold hemagglutination is the early determination of, and then maintenance of, body temperature above that highest temperature (critical temperature) at which the cold antibody reacts.

Bracken et al (9) described cardiopulmonary bypass in two patients with cold agglutinins that had gone undetected prior to surgery. In one patient, a 67-year-old man, the red cells in the cardioplegia heat exchanger were clumped and separated from the plasma, and the patient developed hemoglobinuria. On the evening of surgery, the

patient was noted to have a cold pulseless left leg and underwent a bedside revascularization procedure. He died on the second postoperative day of hemodynamic compromise. The authors commented that it is not clear that cold agglutinins were directly related to the terminal event.

Holman et al (10) reported a patient who developed intracoronary agglutination of the blood cardioplegia solution. The patient was a 69-year-old man with severe pulmonary dysfunction and class IV angina pectoris who was referred for bypass grafting of a proximal stenosis of the anterior descending artery. During surgery, the heart was arrested using a 4°C blood cardioplegia solution, and agglutinated blood was found when the anterior descending artery was incised. Postcardioplegia reperfusion of the heart was begun with a blood cardioplegia solution delivered at 37°C under controlled conditions of flow and pressure. Postoperatively there was no grossly evident hemolysis and no evidence for myocardial necrosis. The patient's convalescence was uneventful. It should be noted that the patient's cold agglutinin was an anti-I that had an agglutination titer of 256 at 4°C and a titer of 4 at 24°C, but did not react at 30°C or 37°C. The fact that the cold agglutinin was of low thermal amplitude perhaps mitigated against the development of complications.

Stalker (11) reported that clumps of agglutinated RBCs may plug the microcirculation and cause myocardial necrosis, and Davidson et al (12) reported hepatic infarcts in mice injected with anti-erythrocytic serum.

Shanian et al (1) stated that cold-mediated erythrocyte agglutination within the coronary microcirculation might lead to inadequate distribution of cardioplegic solution, poor myocardial protection, and perioperative infarction. They cautioned that, unless cold antibodies are identified prior to surgery, or by the surgeon or perfusionist during bypass, such sequelae of microscopic RBC agglutinates may be attributed to other causes. Indeed, the numerous other causes of hemolysis during cardiopulmonary bypass, including mechanical trauma (13), will likely be considered before testing for the presence cold agglutinins with a high thermal amplitude.

Although not related to surgery, other instances of exacerbation of CAS with exposure to cold have been reported. Niejadlik and Lozner (14) described a patient who developed acute, severe hemolysis after being placed on a cooling mattress. The patient was a 51-year-old white female who was hospitalized with fever and a right lower lobe pneumonia. Her hematocrit on admission was 44% but, after being placed on a cooling mattress, signs of intravascular hemolysis developed with marked hemoglobinuria, and her hematocrit decreased to a low of 16%. *Mycoplasma pneumoniae* infection was documented and cold agglutinins were present at a titer of 25 at 4°C, 32 at room temperature and 8 at 37°C.

Colmers and Snavely (15) reported a patient with primary atypical pneumonia and cold agglutinin syndrome with a cold agglutinin titer of 1,280 whose hemoglobin decreased from 7.5 to 4.5 gm/dl overnight following three general body sponges using iced alcohol. The drop in hemoglobin was accompanied by passage of dark-brown urine. After recovery from her pneumonia and hemolysis, the authors performed an experiment in which the patient's right arm was immersed for 15 minutes in ice-cold water containing pieces of ice. A blood specimen was drawn immediately before immersion of the arm, and then 15 minutes after cessation of immersion and at 15-

minute intervals thereafter. The control and the 120-minute serums were completely free from any trace of hemoglobin on gross visual inspection. The 30-minute specimen was markedly hemolyzed, and the 45-minute specimen showed somewhat less marked hemolysis, as determined visually and by spectral analysis. The patient did not develop hemoglobinuria suggesting that the systemic hemoglobinemia did not reach a sufficient concentration to appear in the urine.

Identification of Patients at Risk.

Since cold agglutinins may be detected in the serums of almost all individuals, the critical problem is to decide which characteristics of a given patient's cold agglutinin would warrant special precautions during surgery. This question cannot be answered precisely, but special precautions would seem important when a patient has a cold antibody-induced AIHA. Although cold-reactive antibodies are not routinely characterized in detail in the blood transfusion service, if the antibodies have a high enough thermal amplitude to cause AIHA, they will ordinarily be noticed during routine compatibility test procedures. Also, for patients who have hemolytic anemia, one would hope that a diagnosis of CAS would have been made prior to surgery on the basis of clinical and laboratory findings (see Chapters 1, 2, 5 and 6).

For patients without hemolytic anemia, the thermal amplitude of the antibody (the highest temperature at which agglutination occurs) is probably the best guide to possible complications during surgery. The thermal amplitude can be determined in the hospital's transfusion service and this procedure should be carried out whenever strong autoagglutination occurs at room temperature. Antibodies that are reactive at temperatures of 30°C or above are capable of causing hemolysis (see Chapter 5) and special precautions would seem to be warranted during hypothermia, even though the manifestations of hemolysis may be minimal to none prior to exposure to cold.

In some cases, autoagglutination will first be noticed in the operating room (4;8;8-10;16). Indeed, Dake et al (16) and Bracken et al (9) have recommended that observation of the blood cardioplegia system for agglutination before cardioplegia administration and systemic cooling be a routine part of the perfusion checklist.

Patients with Cold Agglutinins Who do not Appear to be at Risk.

Normal persons may have cold agglutinins that react at 4°C with a titer of ≤ 32 and with a thermal amplitude of $< 20^\circ\text{C}$. Although cold agglutinins reactive up to room temperature ($\sim 20^\circ\text{C}$) might seem to be of potential significance during hypothermic surgical procedures, there is an impressive lack of reports of complications caused by such antibodies even though they are quite common (17). Indeed, there is general agreement that patients with low-titer, low-thermal amplitude antibodies may undergo operation without any change in routine management plan (18). The thermal amplitude of the cold agglutinin is of particular significance as indicated by the data of Bracken et al (9) who reported 19 patients who had cold agglutinins with titers of 64 to 512 at 4°C, but found that only 3 of these reacted at 25°C. Moore et al (19) stated that patients with titers of ≤ 32 at 4°C and no detectable agglutination at $\leq 28^\circ\text{C}$ tolerated hypothermia

well. However, Moore studied only 5 patients who had strongly positive agglutination in the cold, and only one had an antibody that reacted as high as 23⁰C.

AuBuchon et al (13) studied 16 patients undergoing hypothermic extracorporeal circulation. They found that total extracorporeal circulation time was significantly correlated with a rise in hemoglobin during the procedure, but no correlation was noted between the extent of hemolysis and the presence of cold reacting autoantibodies which were present in 12 patients at 22⁰C or below.

That patients with abnormal cold agglutinin titers requiring special management in hypothermic surgery are unusual is indicated by the data of Bracken et al (9). They reviewed their data regarding adult patients seen over a 1-year period. Only 19 of 504 patients had a titer of ≥ 64 , and, of these, agglutination occurred at 25⁰C in only 3 (tests were performed at 4, 25 and 37⁰C only).

Management.

Hematologists, transfusion medicine specialists and cardiovascular surgeons who identify patients at risk should collaborate to develop a protocol for management. It is prudent to do this in advance of need, especially since cold agglutinins may not be detected prior to surgery in some patients (4;8;8;9;16). There have been a plethora of published accounts recommending various approaches to management of patients who require cardiac surgery and who have cold autoantibodies (1;2;4;6;8-10;16;18-36), including several reviews (2;6;18;37).

Reported techniques of cardioplegic management (37) include warm ischemic arrest (simple aortic cross clamping), warm blood cardioplegia, and the use of a combination of warm and cold crystalloid cardioplegia. In general, cold blood cardioplegia is not appropriate since one would expect significant agglutination in the coronary circulation. The alternative is to use crystalloid hypothermic cardioplegic protection. To avoid the exposure of blood to hypothermic solution in the coronary system, warm crystalloid cardioplegia can be used to flush the coronary circulation clear of blood; this is then followed by cold crystalloid cardioplegia to induce myocardial hypothermia. Toward the end of the procedure, the heart may be rewarmed by warm crystalloid cardioplegia before the cross clamp is removed.

More recently, continuous warm blood cardioplegia (38-41), which can be delivered antegradely (29;42;43) or retrogradely (31;33), has been utilized. This procedure obviates the need for hypothermia and is recommended by a number of authors in this setting (18;31;35;44).

The Role of Plasma Exchange in Preparation for Surgery.

Plasma exchange has been used as adjunctive therapy in some patients (2;20;32;34). However, this procedure requires special techniques since it must be performed at temperatures above the cold agglutinin's thermal amplitude to avoid *in vitro* cold agglutination (20;28;45). Also, the procedure is not reliably effective (32;46;47). (Also see Chapter 11).

Klein et al (20) used plasma exchange before surgery for a patient with an anti-I cold agglutinin. The antibody reacted strongly with RBCs at 15°C, 22°C, and after papain treatment at 37°C; in addition, it agglutinated several panel RBCs in saline at 30°C and occasionally reacted with saline-suspended RBCs at 37°C. The titer at 22°C was reduced by plasma exchange from 4 to 1. During surgery, body temperature was lowered with the core temperature of 29°C as measured with an esophageal sensor. There were no adverse effects during or after hypothermia. As Klein and colleagues point out, they could not be sure that difficulties would have developed had plasma exchange not been performed.

Beebe et al (32) described a case in which plasma exchange was only minimally effective. Beginning 10 days before surgery, the patient received plasmapheresis every other day for five total treatments with each treatment exchanging 1.25 plasma volumes with an equal volume of 5% albumin. The cold agglutinin titer decreased from 4,096 to 512 the day before surgery, but on the morning of surgery, the cold agglutinin had rebounded to 1,024. The patient had chronic CAS but was managed throughout surgery for splenectomy and cholecystectomy by intraoperative forced air convection warming; esophageal and peripheral temperatures were maintained above 37°C throughout surgery and she did not have an exacerbation of her hemolysis.

In the case reported by Park and Weiss (2), the patient had a cold agglutinin titer of 10,000 at 4°C and 5,000 at 20°C but did not have evidence of hemolysis. Plasmapheresis was performed 1 day before surgery and produced "an eight-fold reduction in titers." Body temperature was maintained above 35°C throughout coronary artery bypass grafting, which was performed during a 72-minute normothermic cardiopulmonary bypass at 36 to 37°C. No ventricular fibrillation occurred, and no hemolysis, hemagglutination, myocardial infarction, or organ damage resulted.

Zoppi et al (34) reported a 53-year-old man with abnormally elevated cold agglutinins who was treated by two one-volume plasma exchanges. There was a reduction of the titer of the cold agglutinins against group O RBC at 4°C from 128 to 32, but the titers of 8 at 30°C and 2 at 37°C were not affected. The patient was successfully operated and was discharged on the 16th postoperative day.

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