What the cardiac surgeons have to know about cold agglutination management

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Cold agglutinin has specific importance in cardiac surgery field due to routine use of the systemic, topical hypothermia in cardiopulmonary bypass and cold cardioplegic solutions (4–12°C). We describe a case of coronary artery bypass in which cold agglutinin was detected intraoperatively; hence, cardiopulmonary bypass and myocardial protection strategies were changed. A simple and not expensive test is introduced to screen these patients before operation, as screening is not routine before cardiac surgery in many heart centers. In addition, we provide a literature review for surgical consideration and highlight some important concerns that need to be addressed.

Keywords:
cardiopulmonary bypass, cold agglutinin, hemolysis, hypothermia

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Introduction

Cold agglutinin (CA) has specific importance in cardiac surgery field due to routine use of the systemic, topical hypothermia in cardiopulmonary bypass (CPB) and cold cardioplegic solutions (4–12°C). The consequences of autoantibody activation against surface antigens of erythrocytes during hypothermia are hemagglutination, microvascular occlusion, hemolysis, and organ failure. Avoidance of cold environment is the only prophylactic way, as it has no specific treatment. Data regarding the points of cardiac surgery in patients with CA are limited and generally restricted to case reports or small series.

Although it is rare, CA screening is not routine before CPB in many heart centers, but its potentially lethal complications persuaded the surgeons always think about it. We describe a case of coronary artery bypass in which CA was detected intraoperatively; hence, CPB and myocardial protection strategies were changed.

Case report

A 65-year-old man was referred with ischemic heart disease for coronary bypass graft. His coronary risk factors were hypertension and hyperlipidemia. Routine cold antibody screening is not performed in our center. The operative plan was three grafts (one arterial and two saphenous vein grafts) on moderate (30–32°C) CPB.

It was noted after addition of blood to cold cardioplegic solution (ice content) that the erythrocytes were clumped and separated from the plasma in a few seconds, before inducing systemic cooling. At first, activated clotting time was rechecked (550 s). With the clinical suspicion to CA, 2 ml of heparinized patient's blood was added to an ice cube in a plate; macroscopic hemagglutination appeared again.

We decided to continue the operation with normothermic CPB and intermittent antegrade tepid blood cardioplegia. Anesthetic agents and fluids were warmed. The postoperative hemodynamic status was stable and uneventful. No signs of hemolytic or vaso-occlusive complications were seen postoperatively. The patient had no symptoms related to CA (such as acrocyanosis) as he was asked retrospectively. The subsequent blood examination confirmed the presence of CA (1 : 256) at 4°C.

Discussion

CA is predominantly immunoglobulin M (IgM) autoantibodies that can be activated and react with surface antigens on the erythrocytes at low temperatures. This can lead to hemagglutination at low temperature (IgM affinity is temperature dependent); disagglutination occurs quickly on rewarming (due to decreased activity of IgM). The antigen–antibody complex activates complement and is followed by complement-mediated hemolysis on rewarming [1–7]. The characteristic of CA is rapid reversibility of both antibody activation and agglutination on rewarming, presence of high antibody titer at 4°C and low antibody titer at 37°C [2,8–10].

Approximately, CA has been diagnosed in 1 : 75 000 of general population. The presence of low-dose

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CA in blood is seen in most healthy individuals, and under physiologic body temperature it seldom causes important problem. Its presence is not usually recognized and it has no effect on daily living, because its activation is only at low temperature [4,10–13]. Symptomatic CA depends on temperature amplitude, the temperature below which red blood cell clumping occurs, and the IgM titer [4,13,14].

CA disease may occur as a primary or secondary process. Primary or idiopathic CA disease usually occurs in the old-aged group. It is frequently well tolerated and asymptomatic without need for a specific treatment. Secondary CA disease usually occurs in the setting of an infectious process (e.g. mycoplasma, viral, bacterial, and parasitic), an underlying lymphoproliferative disorder and malignancy [3,4,6,7,10–12].

Activation of CA during CPB can lead to sludging, impaired microcirculation, hemolysis, and thromboembolism in various organs. It can be diagnosed intraoperatively as intracoronary thrombosis, incomplete cardioplegic delivery, visible agglutination in cardioplegia circuit, or high pressures in the CPB circuit at the inlet to membrane oxygenator. Clinical results can include cerebral or myocardial infarction, hepatic or renal failure, hemolysis, persistent hemolytic anemia, and intravascular occlusive crises. Perioperative myocardial infarction is the result of both agglutination pattern in coronary arteries and inadequate myocardial protection due to impairment in cardioplegic distribution [4,6,10,15].

The reported incidence of CAs among screened cardiac surgical patients is between 0.3 and 4% [3–5,7,15,16]. Neither sufficient anticoagulant nor hemodilution during CPB is protective against agglutination and hemolysis [4,5,10]. The management of these patients needs a multidisciplinary team approach, including hematologist, anesthesiologist, intensivist, perfusionist, and surgeon.

There are a number of strategies for intraoperative management of these patients. Literature review shows in patients with low IgM titer and low temperature amplitude that mild hypothermic CPB is safe, and minimal changes to routine practice are required to preserve the core temperature above temperature amplitude [3,4,7,10,12,13,16]. However, induced CPB hypothermia can cause hemagglutination in patients with high IgM titer and high temperature amplitude. Appropriate management may include uneventful cardiac surgery in these patients [2,3,10]. There are two options to avoid this condition: the IgM titer should be reduced or the core temperature should be kept warmer than the thermal amplitude [3,9]. Patients with known CA disease should undergo laboratory testing, including CA titer and thermal amplitude measurement and hematology consult before cardiac surgery [12].

In secondary and transient form of CA, it is suggested to postpone the elective cardiac surgery and frequent measurement of thermal amplitude and IgM titer to decide when surgery can be performed safely [2,13].

To decrease IgM titer, if CA was detected preoperatively, high-dose IgG was suggested just before surgery. It prevents the interaction between IgM and surface antigens of erythrocytes, by covering these antigens [5,14]. The use of plasma exchange for temporary IgM removal is recommended before surgery, especially for patients requiring deep hypothermic arrest [3–5,10,11].

Cardiopulmonary bypass strategies in CA setting

Careful temperature monitoring should be assumed to keep the systemic perfusion temperature above the thermal amplitude of agglutinin activity. The temperature of the operating room should be increased to preserve normothermia during operation and warming mattress should be placed on the operating table. Anesthetic gases could be humidified. The intravenous fluids, blood products, and prime fluid should be warmed [2,5].

Myocardial protection strategies in CA setting

The recommended cardioplegic solutions are normothermic ischemic arrest with warm crystalloid cardioplegia, warm blood cardioplegia and warm retrograde myocardial washout, and cold crystalloid cardioplegia and intermittent cross-clamping with or without fibrillatory arrest [3,4,16]. To decrease myocardial temperature, bicaval cannulation with tourniquets and prevention of heart contact with the descending aorta and other mediastinal structures (by leaving a pad in the posterior pericardium) were suggested. The heart temperature should be sufficiently rewarmed (37°C) to be more than of thermal amplitude at the time of aortic clamp removal [2,4,5,10,14].

There is a controversy about the necessity for routine preoperative screen test. Recently, Jain *et al.* [7] suggested that, in the absence of CA history, the routine CA screen should not be performed as its incidence is low (0.3–4%), poorly specific for true CA with remarkable cost. We do not check for CA routinely in preparation tests of cardiac surgery. Moreover, cold-induced circulatory symptoms are not usually asked by the surgeons before operation. It is hypothesized that a part of unexplained postoperative strokes, low cardiac output, and renal failure may be related to unrecognized CA. There were case reports in which CA was diagnosed by inspection of intracoronary thrombosis, although it was immediately changed to normothermic CPB but was associated with

increased morbidity and mortality, despite all efforts. As the probability of simultaneous occurrence of the agglutination in other organs was high, it may be better that we always remember its presence [2,3,9,15].

It is suggested to keep heparinized patients blood in contact with ice cube before operation in all cardiac surgery patients. This is an in-vitro simple test instead of routine use of expensive Coombs test and electrophoresis. If there is concern, confirmation by the cold antibodies measurement can be followed. Routine use of this test may be worthwhile to detect CA *in vitro* before systemic cooling is begun in patient with unsuspected CA.

Conclusion

The importance of early detection of CA is appropriate preparation of the patient, CPB strategy, operating room, and equipments to prevent intraoperative hemagglutination. Cold agglutination is a rare but potentially lethal complication; hence, it is suggested the surgeons always remember it.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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