



Original Research

The Role of Cold Agglutinins Screening in Cardiac Surgery: Necessity or Redundancy?

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Abstract

Objectives: This study aims to determine the prevalence of cold agglutinins (CA) in patients undergoing cardiac surgery in the Turkish population, to draw attention to the importance of preoperative diagnosis, and to increase clinicians' awareness of cold hemagglutinin disease (CHD).

Methods: 4273 patients who underwent elective cardiac surgery between 2012-2022 were examined. All patients were routinely screened for CA. Patients were divided into two groups: 18-49 years old (Group 1) and over 50 years old (Group 2). Prevalence analysis was performed by comparing these age groups and genders.

Results: Among all patients, CA was positive in 390 (9.12%). There was no difference between group 1 and group 2 in all patient groups and women. However, CA was found to be higher in group 2 in men compared to group 1 (n=154 (8.9%) and n=65 (6.6%), respectively), p=0.47). CA was found to be higher in women compared to men (n=171 (10.9%), n=219 (8.07%), respectively), p=0.015).

Conclusion: We found that CAs were considerably high in patients undergoing cardiac surgery in the Turkish population. CA is important for cardiac surgery where hypothermia is used, and we believe that this pathology should be routinely screened in the pre-operative period. Due to these rates that cannot be ignored, the clinical awareness of the heart team about CHD should be increased.

Keywords: Autoimmune disease, cardiac surgery, cold agglutinin, cold agglutinin disease, hypothermia

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Cold agglutinins (CA) are autoantibodies that can be found in humans and are rarely of clinical importance. They may be hereditary, idiopathic, or acquired due to malignancies or infections.^[1] Cold hemagglutinin disease (CHD) involves agglutination and hemolysis of red blood cells (RBCs) through complement activation at low temperatures. Most cold agglutinin antibodies are polyclonal and benign, but monoclonal ones are usually pathologically defined. Benign autoantibodies can cause hemagglutination and complement fixation below 25°C, whereas monoclonal and

pathological ones can activate complement fixation even at 30°C to 37°C.^[2-4] This is particularly important in cardiac surgery, where hypothermia and cold cardioplegia procedures are performed. Increased viscosity and microthrombosis can lead to cerebral or myocardial infarction, hepatic or renal failure, end-organ damage, and severe hemolysis.^[4,5] There is no consensus yet for these patients, but many studies recommend mild hypothermia and warm cardioplegia during surgery in patients with high-titer autoantibodies.^[2]

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CA is rare and is not included in routine preoperative screening programs in many centers. In addition, this rate may vary among populations. We estimate that the frequency of these CAs is higher in the Turkish population. Since hypothermia is routinely used for many operations in cardiac surgery, the operative strategy changes especially in patients with CA positivity. Preoperative recognition of these patients can prevent catastrophic complications by taking precautions. Therefore, in our clinic, CA is routinely investigated in all patients before cardiac surgery. This study aims to determine the prevalence of CA in patients undergoing cardiac surgery in the Turkish population, to draw attention to the importance of preoperative diagnosis, and to increase clinicians' awareness of CHD.

Methods

This study was designed as a retrospective observational study including a total of 4273 patients. All patients who underwent elective cardiac surgery in our clinic between June 14, 2012, and February 5, 2022, were included in the study. Patients under the age of 18, emergency surgeries, and those who underwent surgery without the use of cardiopulmonary bypass (CPB) were excluded from the study. All patients had their basic demographic data recorded and in addition to the routine preoperative cardiac evaluation performed in our clinic, CA tests were also performed. Laboratory evaluation included examination of specific temperatures such as 4°C, 22°C, 30°C and 37°C. A thermal amplitude of 30°C was considered clinically significant in patients with positive CA titers of $\geq 1:64$. Patients were first divided into two groups; Group 1: those aged 18-49 years and Group 2: those aged ≥ 50 years. They were also divided into two groups male and female. Prevalence analysis was performed by comparing CA between these groups.

In our clinic, instead of routine hypothermic CPB, we applied normothermic CPB and intermittent antegrade warm cardioplegia infusion in patients with positive CA. The temperature was kept between 32-36 depending on the type of operation. We also tried to keep the patient warm by using blankets throughout the operation. No patient required total circulatory arrest.

This study was approved by the Istanbul Medipol University Non-interventional Clinical Research Ethics Committee (date: 16.10.2024, decision no: E-10840098-202.3.02-6341). Artificial intelligence-assisted technologies in the production of submitted work were not used. Written informed consent was obtained from the patients. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Data were analyzed by using SPSS software version 20.0 (IBM, USA). In descriptive statistics, categorical variables were expressed as frequency (n) and percentage (%). The normality of distribution was assessed by the Kolmogorov-Smirnov test. For numerical variables, differences between patients and controls were tested using t test for parametric data or the Mann-Whitney U test for non-parametric data. Categorical variables were analyzed using the Pearson χ^2 test and Fisher's exact test for parametric and non-parametric data, respectively. The level of statistical significance was set at $p < 0.05$.

Results

The age groups, genders, and CA results of the patients are shown in Figure 1 and 2. In the whole patient group including a total of 4273 patients, CA was detected as positive in 390 (9.12) patients. After the patients were divided into Group 1 and Group 2, first of all, all patients were compared in terms of CA rates and no difference was found between the groups

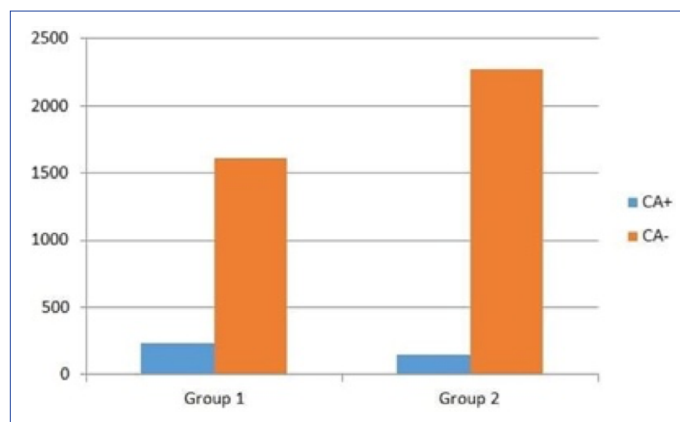


Figure 1. Comparison of cold agglutinins among all patients by age group.

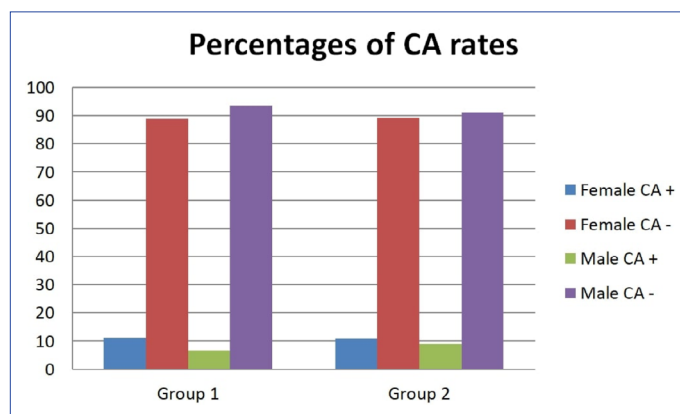


Figure 2. Comparison of percentages of CA rates among groups according to gender.

($n=238$ (9.5%) and $n=152$ (8.6%), respectively, $p=0.177$). Similarly, no difference was found between the groups in terms of CA rates in female patients ($n=87$ (11.1%) and $n=84$ (10.9%), respectively, $p=0.47$). In male patients, CA rates were found to be significantly higher in Group 2 compared to Group 1 ($n=154$ (8.9%) and $n=65$ (6.6%), respectively, $p=0.47$).

The patients were divided into two groups male and female and compared again. When the patients with positive CA were compared according to gender, it was found to be significantly higher in females ($n=171$ (10.9%) and $n=219$ (8.07%), respectively), $p=0.015$).

Discussion

CAs are cold-reactive autoantibodies, usually of the IgM subtype, that bind to RBC surface antigens at low temperatures, causing agglutination and hemolysis.^[6] CHD is an autoimmune disease caused by these antibodies.^[7] CA antibodies are present in many people, but their clinical significance depends on titers and thermal thresholds. Benign autoantibodies can cause complement activation at low temperatures, while pathological ones can cause complement activation even at normal body temperature. There is no widely accepted definition of titer levels yet. Lee et al.^[8] suggested that titers lower than 1:32 are low and titers higher than 1:128 are high. Mostly, patients with a positive CA titer of $\geq 1:64$ are considered clinically significant for disease activity.^[4] In our clinic, a positive titer of $\geq 1:64$ is considered clinically significant. Although titers greater than 64 are considered high, hemolysis is rarely seen unless it is greater than 1000.^[2]

CPB, hypothermia and cold cardioplegia are routinely used in many cardiac surgical operations. Therefore, the presence of these antibodies in this patient group is important in terms of possible perioperative and postoperative complications. Many catastrophic complications such as increased viscosity, microthrombosis, cerebrovascular accident, myocardial infarction, hepatic failure, renal failure, severe hemolysis, CPB circuit interruption during surgery, and inadequate perfusion can be seen in patients with CA.^[4,5,9-11] If not diagnosed earlier, CA can lead to life-threatening events. Therefore, recognition of this disease and timely interventions can be life-saving for patients.

CHD is known to be a rare disease, but screening of patients undergoing cardiac surgery has reported a significant incidence of approximately 0.8%-4%.^[12] These rates may differ between races and societies. We believe that this rate is higher in Turks. We designed this study because there are not enough studies on this subject especially because there is no data on this subject in Turkish society to the best of our knowledge.

We found CA levels to be higher than expected. In this study, we examined a total of 4273 patients who underwent cardiac surgery and found CA positive in 390 (9.12%) patients. It has been reported that the incidence of CA increases especially after the age of 50.^[13] Therefore, we divided the patients into two groups according to this age. We found it to be 9.5% in the 18-49 age group and 8.6% in those aged ≥ 50 . We did not find any difference between age groups, in the entire patient group and women, but we found that CA was higher in men aged ≥ 50 compared to those aged 18-49. In the literature, it has been reported that cold agglutinin disease is more common in the elderly.^[14] These results are significantly higher than the findings in the literature.^[12] The presence of these antibodies may not be clinically significant for many patient groups whose body temperature does not drop. However, it is extremely important for cardiac surgery, where hypothermia is routinely applied in many types of operations. In particular, agglutination and hemolysis that may occur in the CPB device during the operation can have fatal consequences. Therefore, knowing the presence of these antibodies and the disease before the operation will be life-saving.

We also found that CA was significantly higher in women than in men (10.9%-8.07%, respectively). Some studies have shown that women are slightly more affected by cold agglutinin disease than men.^[15] This indicates that this pathology should be investigated more carefully, especially in women.

Diagnostic methods include indirect hemagglutinin test, cross-matching, peripheral blood smear, and Coombs test.^[7] However, the role of routine preoperative screening before cardiac surgery is currently controversial. Routine screening is not performed by many centers. Screening is generally performed in many centers in cases of unexplained hemolytic anemia, autoimmune diseases, lymphoproliferative disorders, or symptoms suggestive of CHD. However, since we believe that these rates are higher than expected, we perform routine screening in our clinic. The results we found are significantly higher than the known population average, supporting our hypothesis. Therefore, we think that this test should be included in the routine preoperative screening program. Although cost is an important point, screening for this pathology, which is seen at such a high rate and has the potential to cause serious complications, will be beneficial in terms of improving postoperative outcomes. Another important point is that this disease may have been detected at a low rate because it is not in the routine screening program. We think that if routine screening were performed, it could have been detected at a higher rate, as in this study.

Interventions for patients with positive CA or detected during surgery are life-saving. Management and planning should be personalized according to the type of operation and patient risk factors. First of all, the patient should be evaluated for an operation that can be performed without CPB. If CPB is to be used, normothermia with warm cardioplegia is recommended for many operations.^[2] We also applied normothermic CPB with intermittent antegrade warm cardioplegia infusion in patients with CA positive. If the operation requires total circulatory arrest, the combination of plasmapheresis and hypothermia above the temperature threshold is a safe choice.^[4] Antibody titers can be reduced with preoperative plasmapheresis. Some studies suggest the use of glucocorticoids before surgery in patients with high titers.^[16] Total washout can be done before surgery.^[17] It is important to wash the coronary arteries with warm cardioplegia.^[11] This can prevent hidden microembolism. The temperature in the operating room can be increased, and the patient can be warmed with blankets. If CAs are thought to be caused by a recent viral infection, the operation can be postponed for 2 weeks in suitable patients to allow the antibodies to disappear.

Limitations

Since the primary aim of this study was to determine the frequency of CA, detailed data on patients' preoperative routine blood tests and intraoperative and postoperative complications are not included in the study. In addition, no detailed laboratory studies were performed to determine whether CA antibodies were benign or pathological. Another important point is that the false positive rates for CHD are considerable. However, the results of this study are still important in guiding future studies and in terms of including this screening test in the routine program.

Conclusion

We found that CAs were considerably high (9.12%) in patients undergoing cardiac surgery in the Turkish population. We found that CA was higher in men over 50 years of age than in those between 18-49 years of age. In addition, CA positivity was higher in women than in men. CA is important for cardiac surgery where hypothermia is used, and we believe that this pathology, which we found to be seen with such a high frequency, should be routinely screened in the preoperative period. In addition, due to these rates that cannot be ignored, the clinical awareness of the heart team about CHD should be increased.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Non-interventional Clinical Research Ethics Committee (date: 16.10.2024, no: E-10840098-202.3.02-6341).

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