Notes on Cold Agglutinin Disease for Cardiac Perfusion Practice

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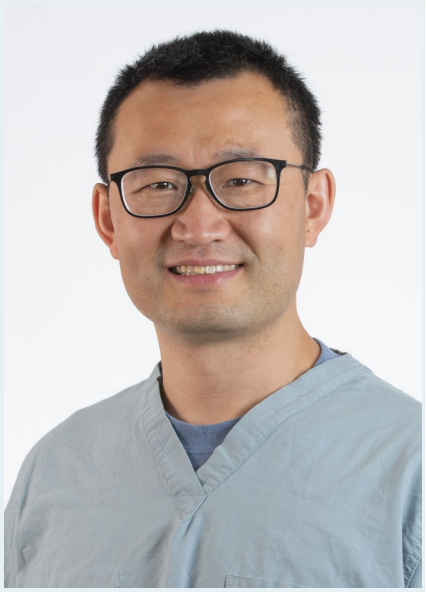

Cold agglutinin disease (CAD), a subtype of autoimmune hemolytic anemia, is a rare (approximately 1:300,000) disorder that is characterized by the pathological destruction of red blood cells (RBCs) by circulating cold-sensitive antibodies, also known as cold agglutinins (CAs). These antibodies, usually immunoglobulin M (IgM), are present in most people but are rarely of clinical significance at normothermia.[1] The antibodies become active at temperatures <30 °C and then bind RBCs into clumps (agglutination), which eventually cause microvascular occlusion and systemic hemolysis.[2] Therefore, CAD can lead to anemia and other related symptoms including tiredness, dizziness, headaches, cold hands and feet, pale skin, dark urine, chest pain, and even heart failure. CAD is also called cold hemagglutinin disease, cold agglutinin syndrome, and cold hemagglutinin syndrome.

Two types of CAD

First described in the 1950s,[3,4] CAD has traditionally been classified as either primary or secondary. The term "cold" is derived from the immunological rather than the clinical features of CAD. Primary CAD is a chronic condition and does not involve an underlying disease. A characteristic clinical manifestation of primary CAD is excessive B lymphocyte proliferation, which causes production of CAs. Production of these antibodies and the resulting symptoms often occur in those 50 years of age and peak in the 70s and 80s.[2] Our knowledge of primary CAD is incomplete. Secondary CAD is the more common form and usually results from an underlying infectious disease such as mycoplasma pneumonia or human immunodeficiency virus (HIV).[5] Drug-induced secondary CAD is uncommon.[2] In both forms of CAD, autoantibodies bind to RBCs, and the antigen-antibody complex induces activation of the complement system and hemolysis.

CAD and COVID-19

In December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China. By March 2020, COVID-19 had spread worldwide, leading to an ongoing pandemic. Patients often present with fever, cough, shortness of breath, fatigue, and loss of smell and taste. CAs have been reported to be of clinical significance in some COVID-19 patients despite the presence of minimal *in vivo* hemolysis, given their frequent need for renal replacement therapy.[6] Because of the high incidence of disseminated intravascular coagulation in critically ill COVID-19 patients[7] and the literature associating CAD with thrombotic events,[8] some investigators have speculated that SARS-CoV-2 infection may cause

CAD.[9, 10] However, more research is needed to better understand the relationship between SARS-CoV-2 and CAD, including complete blood work evaluation in these patients.

CAD and cardiopulmonary bypass

Cardiopulmonary bypass (CPB) and hypothermia provoke a significant physiological disturbance in patients undergoing cardiac surgery, particularly in patients with CAD. The presence of CAs creates a significant risk of morbidity during CPB requiring systemic hypothermia and cold cardioplegia. Recent studies suggest that dysfunction of the myocardium and other end organs, such as the liver and kidneys, is attributed to CAs in patients undergoing hypothermic CPB.[11] Mainly, this occurs because cold temperatures activate CAs, which in turn cause massive hemagglutination, followed by complement fixation, catastrophic hemolysis, and microvascular thrombosis upon rewarming. This situation can lead to intracoronary thrombosis, visible agglutination, and high line pressures in the cardioplegia circuit, as well as insufficient cardioplegia delivery, during cardiac operations.

The incidence of CA-related complications during cardiac surgery is reported to be ~0.8% to 4%.[11] Numerous published case reports have outlined intraoperative management strategies for CAD patients with coronary artery disease (for both off-pump[12] and on-pump[13] procedures), coronary sinus ostial abnormalities,[14] aortic[15] or mitral[16] valve defects, aortic arch aneurysm,[17] and aortic dissection,[18] and for those undergoing organ transplantation.[19, 20] In a few case reports, cardiac surgery in pediatric CAD patients with congenital heart disease has been described.[21, 22] Although intraoperative management strategies remain controversial, CAD patients require extra attention and individualized planning for managing CPB and myocardial protection, and maintaining CAD patients within a categorically safe temperature range is crucial throughout the procedure.

CAD screening before cardiac surgery

As it is essential to know who is at risk due to CAD, every patient scheduled for a cardiac procedure should undergo preoperative screening for CAD before surgery. In addition to the age and infection factors mentioned above, CAD is 1.5 times more common in women than in men.[5] Preoperative symptoms and signs of hemolytic anemia (eg, pallor, jaundice, and hemoglobinuria) are good indicators for laboratory tests such as reticulocyte count and a peripheral blood smear, which can provide a preliminary diagnosis of CAD. Unfortunately, some patients who have no symptoms or signs still could be at risk of agglutination and hemolysis due to non-physiological hypothermic conditions during cardiac surgery. In emergency situations, it is critical to empirically treat patients with signs of CAD, especially if the patient had clotted blood in initial laboratory draws.

Plasma titers of CA and the thermal amplitude test should be used to screen for CAD-positive patients, because activation of CAs closely depends on those two factors. The cold agglutinin titer blood test, also known as the direct Coombs test or the direct antiglobulin test (DAT), is a reliable diagnostic laboratory test for CAD. Healthy individuals often have low serum levels of CAs (about 1:16), but they can safely undergo CPB with little change in practice. Lower CA titers (up to 1:40) are not considered clinically significant[11] and may not pose a risk of agglutination during surgery. However, with higher titers (>1:128), CA activation is more likely to occur.[5] A hematologist's evaluation should be sought in patients with a significantly higher titer. Hemolysis is rarely seen when CA titers are below 1:1000.[13] Patients with CAD would present with laboratory evidence of hemolysis (eg, high lactate dehydrogenase, high bilirubin, and low haptoglobin) and a positive direct Coombs test. In addition to CA levels in plasma, the temperature below which CA activation occurs should be determined preoperatively, thus providing the surgeon and anesthesiologist with an appropriate temperature range for the patient.

Born and raised in China, Liming Luan was a staff scientist in the Department of Anesthesiology at Vanderbilt University Medical Center (VUMC) before being accepted as a student at Texas Heart Institute School of Perfusion. During his tenure at VUMC, Liming not only actively maintained his own projects, but also served as a key facilitator, collaborating with each member of the research team. Liming was nominated for the Roger England Research Award, which he won at the 13th Annual Department of Anesthesiology Research Symposium in 2017 at VUMC. Currently, Liming is a student ambassador to the American Academy of Cardiovascular Perfusion.

Management and Treatment

Because of the rarity of CAD, no systematic studies have been conducted to assess its optimal treatment. The primary strategy is to treat the underlying infection and largely depends on the severity of the condition. For clinical perfusionists, CAD patients with high CA titers and a wide thermal range for antibody activation present challenges during CPB. Unfortunately, little is known on how to treat such patients who have severe, life-threatening hemolytic anemia. A common intraoperative management strategy for CAD patients during cardiac surgery is to maintain normothermic CPB or keep systemic perfusion temperature above the thermal threshold of agglutinin activity, while continuously delivering warm blood cardioplegia or cold crystalloid cardioplegia above the thermal amplitude. In addition, anesthetic agents and fluids (including priming fluids) should be warmed, the operating room temperature should be increased, and a warming blanket can be applied.

For patients who require deep hypothermic arrest, preoperative high-volume plasmapheresis[13] (also known as plasma exchange therapy) in combination with intravenous immunoglobulin infusion[23] can be used to significantly reduce CA titers. Previous reports have described multiple preoperative management strategies, such as the use of steroids,[24] rituximab,[25] cyclophosphamide,[26] chlorambucil,[11] high-dose IgG,[27] and eculizumab.[28] These medical therapies are suggested to reduce CA titer or reactivity, but the details of their underlying mechanisms are unclear.

Because CAD is rare and still underdiagnosed in many hospitals, it is difficult to design and conduct randomized clinical trials with adequate statistical power. Nevertheless, several B-cell-directed therapies, such as rituximab, are now available. Novel complement-directed therapies are currently being investigated and appear promising. Potential life-threatening events such as heart attack and stroke caused by CAs warrant better awareness and improved screening for individuals suspected of having these antibodies. As evidence-based therapies for CAD patients are urgently needed, we as perfusion students and perfusionists need to stay abreast of new developments in the field and be vigilant in managing patients during our practice.

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