Cryoglobulinemia is a condition that occurs when there is a presence of a single or mixed immunoglobulins (Igs) in the serum that undergo reversible precipitation at lower than normothermic temperatures, leading to decreased solubility and subsequent microvascular damage. According to the Brouet classification, there are 3 primary types of cryoglobulinemia with type I being a simple cryoglobulinemia consisting primarily of monoclonal IgM with more rarely seen with IgG, IgA, or light chains. Types II and III are considered mixed types, consisting of 80% of cases commonly seen with rheumatoid factors. The most concerning sequelae of cryoglobulinemia include vasomotor neuropathy, nephropathy, and vasculitis causing severe cutaneous ulcerations/necrosis and death. Hypothermia and cold cardioplegic arrest are routine components of cardiac surgery that can precipitate activation of cryoglobulins, resulting in disastrous microvascular damage, cellular lysis, and vascular or extracorporeal circuit thrombosis. Several case reports have identified various approaches to safely perform cardiac surgery; however, the following case and discussion provide a summary and review of strategies for management of patients with cryoglobulinemia who require cardiac surgery. The patient provided written consent for publication of study data and this was approved by the West Virginia University Health Sciences Institutional Review Board (protocol #2006047334; June 23, 2022).

**CENTRAL MESSAGE**
Clinical cryoglobulinemia poses a major risk for cardiac surgery that can be ameliorated through aggressive perioperative management.

**See Commentary on page XXX.**
perfusion. The valve was exposed through a conventional left atriotomy and replaced with a 25-/33-mm On-X mechanical valve (On-X Life Technologies, Inc). The operation was uneventful with crossclamp time of 90 minutes and cardiopulmonary bypass time of 101 minutes. His lactate dehydrogenase and plasma free hemoglobin levels were trended perioperatively as were postoperative cryoglobulinemia titers to assess need for additional plasma exchange. The hemolysis markers and titers remained low, and his hospital course was uneventful. He was discharged home with intravenous antibiotics for his endocarditis, a home steroid dose regimen, and therapeutic warfarin for the new valve on postoperative day 5. He completed his 1-month follow-up and currently remains taking chronic steroids without any residual complications.

**DISCUSSION**

The major concern with cryoglobulinemia in the setting of cardiopulmonary bypass is the risk of activation of the cold agglutinins precipitating the clumping of red blood cells. This can be disastrous and result in major complications, including stroke, cardiogenic shock, and even death as reported by Vela and colleagues. The clinical importance, we reviewed various approaches to perioperative management for these patients to reduce the risk of major complications, including plasma exchange, warm blood cardioplegia, or warm fibrillatory arrest. The series by Agarwal and colleagues in 1995 provided an algorithm for perioperative management based on timing of diagnosis and titers for those identified preoperatively. That study was limited by a majority of patients having cold agglutinin disease, with only 3 patients having the more serious cryoglobulinemia. The more recent series by Yamazaki and colleagues provides a complete review of case reports, including only those with a diagnosis of cryoglobulinemia (n = 14) across several operations such as coronary, valve, and aortic surgery with 3 patients requiring hypothermic circulatory arrest. The series highlights a significant increase in the use of plasma exchange

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**FIGURE 1.** Plasma exchange for type II cryoglobulinemia. Schematic illustrating a patient with type II cryoglobulinemia with monoclonal immunoglobulin M (IgM) and polyclonal immunoglobulin G (IgG) causing neurologic and renal injury undergoing plasma exchange where waste is pulled off and exchanged with albumin and normal saline.
(57%; n = 8 out of 14, pre/intra/post) as well as warm/ tepid blood cardioplegia (93%; n = 13 out of 14) with only 1 reported mortality (7.1% perioperative mortality).\textsuperscript{4,5}

Among the challenges of decision making relates to timing of diagnosis and availability of lab testing for titers (frequently a send-out lab). As was performed for our patient, we believe that preoperative plasma exchange should be performed for all patients with clinical evidence of cryoglobulinemia and when performed within an hour of surgical start time there is a working theory that the body’s immune system will not have time to respond with new formation of cryoglobulins or cold agglutinins. For this reason, we elected to use cold blood cardioplegia, which is our standard practice; however, the use of warm blood cardioplegia or crystalloid cardioplegia may reduce the risk of microvascular myocardial injury. When cardioplegic arrest is not necessary, off pump, pump-assist heart beating, and fibrillatory arrest have all been employed. Finally, given the risks associated with plasma exchange, including coagulopathy and immunosuppression, we elected not to preemptively perform plasma exchange postoperatively and instead monitor the clinical course and serum markers.

CONCLUSIONS

Clinical cryoglobulinemia poses a major risk for patients undergoing cardiac surgery that can be ameliorated through aggressive perioperative management.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The Journal style requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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