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State of the Art in Blood Cardioplegia: Contemporary Evidence, Innovations, and Clinical Implications

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ABSTRACT

Introduction: Blood cardioplegia revolutionized myocardial protection by combining oxygenated blood with potassium and metabolic substrates, thereby enhancing physiological preservation during cardiac surgery.
Objective: To review the historical evolution, physiological principles, and contemporary developments in blood cardioplegia, including delivery strategies, temperature management, and current applications in minimally invasive surgery.
Methods: This narrative review synthesizes key experimental and clinical studies describing the evolution of blood cardioplegia, including major contributions from foundational and contemporary investigators.
Results: Blood cardioplegia evolved from intermittent hypothermic administration to continuous and warm perfusion strategies. Delivery techniques expanded from antegrade infusion to retrograde, alternating, and combined approaches. More recently, hybrid strategies such as del Nido cardioplegia have enabled prolonged myocardial protection with reduced need for repeated dosing, particularly in minimally invasive procedures.
Conclusion: Blood cardioplegia remains a cornerstone of myocardial protection. Contemporary strategies emphasize individualized approaches based on patient characteristics, surgical complexity, and procedural goals.
Keywords: Blood Cardioplegia. Myocardial Protection. Warm Cardioplegia. Del Nido. Minimally Invasive Cardiac Surgery.

Abbreviations, Acronyms & Symbols	
RCT	= Randomized control trial

INTRODUCTION

Myocardial protection is fundamental to cardiac surgery and remains a mainstay of safe procedures that require arrested hearts. The introduction of blood cardioplegia in the late 1970s revolutionized intraoperative myocardial preservation by combining oxygenated blood with potassium and adjunctive agents[1,2]. The fundamental of blood cardioplegia was related to providing more physiological solutions, better oxygen-carrying capacity to myocardial cells, buffering properties, and better metabolic support, adding protection to the myocardial and increasing the safety of open-heart surgeries[3,4].

The improvement of myocardial preservation knowledge has contributed tremendously to the advances in cardiac surgery; however, many questions remain without clear answer leading to different solutions to be administered, variations on temperature, routes of delivery, and persistent scientific debate about the best way to protect the heart against deleterious ischemic effects[5,6].
This review examines the historical evolution of blood cardioplegia, the contributions of key innovators, and the emergence of strategies tailored for minimally invasive procedures and complex cases where long ischemic time are anticipated.

HISTORICAL BACKGROUND

The origins of myocardial protection trace back to 1883, when Sidney Ringer discovery the calcium's role in cardiac contraction[1]. In 1955, Donald Melrose and colleagues introduced potassium-based crystalloid cardioplegia, which initially showed promise

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outcomes. However, it was identified later that the solution caused myocardial necrosis due to very high potassium concentration in the formula[2]. Crystalloid formulations evolved during the 1960s and 1970s, incorporating buffers and substrates, yet lacking oxygen-carrying capacity. During this time, European centers of cardiac surgery favored crystalloid solutions such as Bretschneider's, and centers in the United States of America increasingly adopted blood-based strategies[3].

A major inflection in this evolution occurred with the early work of Salerno's group at McGill University and University of Toronto, whose contributions helped redefine both the physiological rationale and clinical application of myocardial protection. As documented in this manuscript: "Salerno and colleagues advanced continuous cold blood cardioplegia… not only during coronary artery surgery but also with other cardiac procedures such as mitral and aortic valve replacement, ventricular aneurysm resection and others", a major milestone in the field of myocardial protection[3,4]. This work originated during his tenure at McGill University in 1984, where he investigated oxygen delivery in hypertrophied myocardium. His team transitioned from perfluorocarbon oxygen carriers to antegrade continuous cold blood cardioplegia, observing superior myocardial performance despite technical challenges such as distention and reduced visualization due to continuous blood infusion. These early studies laid the physiological foundation for the later paradigm shift toward normothermic solutions[5,6].

Across multiple peer-reviewed sources and decades of clinical practice, Toronto's group contributions appear at every major turning point in the evolution of myocardial protection. The research group reintroduced normothermia into a field dominated by hypothermia, developed and validated continuous warm blood cardioplegia (both antegrade and retrograde), and provided the conceptual framework for warm heart surgery. This research produced seminal work that continues to influence global practice, and its innovations helped shift the field toward oxygenated, metabolically active, continuous perfusion strategies — concepts that remain central to cardiac surgery today.

THE EMERGENCE AND DEVELOPMENT OF BLOOD CARDIOPLEGIA

In 1977, Gerald Buckberg introduced blood cardioplegia by mixing oxygenated cold blood with potassium. His structured protocol included warm induction, cold arrest, a mandatory ischemic interval period, and terminal warm reperfusion ("hot shot"). During those initial years researching blood cardioplegia, important ideas were presented related to oxygen delivery during arrest periods, buffering properties of blood, prevention of myocardial edema, better metabolic intracellular findings, and maintenance of adenosine triphosphate levels[7]. By the 1990s, cold blood cardioplegia had become widely accepted. Intermittent dosing every 20 minutes ensured myocardial protection but introduced intermittent ischemic intervals during aortic cross-clamping[8-10]. After almost one decade from the advent of blood cardioplegia, medical publications lead to a stepwise myocardial protection system, including cold induction, intermittent cold maintenance, retrograde infusion, and warm reperfusion[11].

As an evolution, Toronto's group advanced the study on continuous cold blood cardioplegia, not only during coronary artery surgery but also with other cardiac procedures, such as mitral and aortic valve replacement, ventricular aneurysm resection, and aortic surgery. However, visualization challenged (the surgical preference for a bloodless operative field) during the procedure hindered its acceptance due to continuous blood in the operative field. This research challenged the dominance of hypothermic cardioplegia. Normothermic strategies at induction of arrest improved the metabolic status of the heart and recovery with the hot shot following the period of mandatory ischemia, reducing reperfusion injury.

The concept of continuous warm cardioplegia originated with a research fellow, Robert Cusimano, while working as research resident in the laboratory of University of Toronto. Considering the previous idea of resuscitating the heart with warm induction, he extended this logic quoting: "If warm blood is beneficial at induction and reperfusion, why not maintain the myocardium with warm blood cardioplegia, continuously perfused during arrest?". Also, warm blood had better oxygen delivery capacity due to shift in the oxygen-dissociation curve with cold blood. Clinically, the development of this idea went slowly, with blood cardioplegia solution been warmed up before administration and delivered continuously during surgery, the bold goal behind this strategy was to turn the aortic clamping time irrelevant as the heart was continuously perfused. This was the creation of "warm heart surgery", that led to the publication of the *Warm Heart Surgery* book in 1995, a consolidated global experience with warm blood cardioplegia across all patients undergoing coronary, valve, congenital, and transplant surgeries[12].

In 1995, Calafiore A et al.[13], published the experience with a variation of continuous warm blood cardioplegia. The authors proposed an intermittent warm blood technique single-dose strategy for myocardial protection, relying on warm arrest physiology, long dosing intervals and advocating that it was an easy technique to be adopted due to a simple configuration. The authors showed that warm blood cardioplegia could safely achieve myocardial arrest and intermittent dosing was sufficient for myocardial protection, keeping a bloodless operative field with excellent recovery of ventricular function after reperfusion. This was another contribution shifting from cold crystalloid cardioplegia to blood-based cardioplegia formulas.

Blood cardioplegia and variants gained popularity as excellent options for myocardial protection. However, the debate persists about the superiority of blood cardioplegia over crystalloid solutions. Recent and older randomized control trials (RCTs) comparing cold blood *vs.* cold crystalloid cardioplegia did not show inferiority of crystalloid solution for left ventricular function and similar clinical outcomes (no significant difference in death, myocardial infarction, or low cardiac output syndrome). In 2026, Hasegawa S et al.[14] published the comparison between crystalloid and cold blood cardioplegia for aortic arch surgery. This RCT showed that crystalloid cardioplegia was not inferior to cold blood in providing myocardial protection, evaluated mainly by left ventricular function. The authors analyzed 52 patients who underwent aortic arch replacement, at 1:1 randomization rate (cold blood *vs.* cold crystalloid cardioplegia), and they concluded that crystalloid solution was no inferior to blood cardioplegia for myocardial protection in elective aortic arch replacement, as suggested by comparable postoperative left ventricular ejection fraction.

DELIVERY STRATEGIES

Initially, Buckberg's cardioplegia solution was delivered just through antegrade injection usually in the ascending aorta. Microsphere

studies later demonstrated improved distribution with alternating antegrade and retrograde routes. A pivotal clinical observation occurred when both ports of antegrade and retrograde infusion were inadvertently left open, resulting in continuous simultaneous antegrade/retrograde warm perfusion without adverse effects. Subsequently, it was confirmed the superiority of simultaneous antegrade/retrograde delivery of blood cardioplegia in laboratory studies[15].

The route choice to deliver cardioplegia is driven by case complexity and surgeon experience. RCTs comparing antegrade *vs.* retrograde *vs.* combined cardioplegia delivery strategies are not available, most data are observational. Overall, some concepts are usually accepted; antegrade route is excellent in the absence of severe coronary blockages, retrograde route could better protect post coronary stenotic regions (caveat regarding the protection of the right ventricle and the territory of the right coronary artery), and combined route should be adopted for complex cases (this superiority is more accepted than firmly proved).

MINIMALLY INVASIVE SURGERY AND DEL NIDO CARDIOPLEGIA

Minimally invasive cardiac surgery expanded through thoracotomy, partial sternotomy, and peripheral cannulation. High-volume centers adopted these techniques due to their steep learning curve. Intermittent cold blood posed challenges in minimally invasive settings because reinfusion every 20 minutes was necessary to ensure adequate protection leading to interruption of the procedure. The rational for myocardial protection during minimally invasive cardiac surgery was the use of a solution that could be administered as a single-dose and low-interruption intervals for new infusions.

In this scenario, del Nido type blood cardioplegia gained popularity in adult cardiac surgery prolonging cardiac arrest with fewer interruptions, lower myocardial injury markers, reduced need for defibrillation, and even improved clinical outcomes in comparison with other cardioplegia solutions.

Del Nido cardioplegia was developed by Pedro del Nido while working at University of Pittsburg. The work of Karin Wittnich, studying immature myocardium in the experimental research laboratory in Toronto, contributed to del Nido observations. The Toronto research group was working on immature hearts and felt that the metabolically needs of myocardium in neonates might be different than adult hearts, requiring new strategies for myocardial protection[16].

The rationality of del Nido's cardioplegia was directed to solve this clinical problem related with the protection of immature myocardium, aimed for a solution that would be able to provide long lasting cardiac arrest with single dose, reducing cell injury and ultimately improving myocardium protection and clinical outcomes. The formulation evolved from the research lab to surgical utilization with a combination of lidocaine, magnesium, mannitol, and bicarbonate in a 1:4 blood to crystalloid ratio[17,18].

Initially used in congenital surgery, del Nido cardioplegia later expanded to the adult population, not without reservations from many surgeons, who felt that the effects of cardioplegia may be good at surgery, but it might lead to severe myocardial dysfunction with time, leading to heart failure. Despite this, del Nido cardioplegia slowly gained popularity in adult patients during conventional surgery and it was later introduced into minimally invasive valve procedures, as it allowed longer periods of ischemia without reperfusion[19].

Del Nido solution can provide prolonged diastolic arrest with a single dose, the composition of this solution involves sodium channel blockers (slow depolarization), calcium modulation (reduces the level of intracellular calcium), bicarbonate (maintains physiological pH), and lower crystalloid volume (reducing myocardial edema). The idea of mixing the solution with blood is to achieve better oxygen delivery, physiological osmolarity, pH control, and less cellular deformity during ischemia. The classic del Nido solution is crystalloid dominant (1:4) while blood-based reverse this ration (four parts of blood: one part of del Nido; 4:1) with addition of the following components to the formula: potassium, lidocaine, magnesium, mannitol, and bicarbonate[20,21]. The main goals with blood-based del Nido solution are to reduce the crystalloid volume given during cardioplegia infusion and to add blood advantages when mixed in the solution.

The utilization of del Nido blood-based cardioplegia has been accepted as an excellent choice for myocardial protection, including a vast field of indications from pediatric to adult patients, complex procedures, and minimally invasive surgery with limited access to the heart due to small and alternative incision in the chest wall. It has been recommended as the initial dose of 20 ml/kg that can be delivered antegradely, retrogradely, or in combination. The redosing interval could range from 60 to 90 minutes (for complex cases, some surgeons advocate redosing every 45 - 60 minutes). Usually, the redosing volume corresponds to half of the initial dose.

MODERN PERSPECTIVES

Blood cardioplegia remains central to myocardial protection, offering flexibility in temperature, delivery route, and dosing strategy. Warm and cold variants coexist, each suited to specific clinical contexts, and del Nido cardioplegia has emerged as a valuable alternative, particularly where single-dose strategies reduce procedural interruptions. Potential indications to using blood cardioplegia are severely depressed left ventricular function, hypertrophic ventricles, recent myocardial ischemia, and pediatric and neonatal surgery[22-23].

Further research is still needed to better evaluate the role of blood cardioplegia during harvesting for transplant. In this situation, it seems that long-acting crystalloid solutions are still the method of choice for heart preservation, with a high-volume transplant center using histidine-tryptophan-ketoglutarate (Custodiol®) protocols.

Currently, we can find some aspects that deserves some consideration for future improvements in myocardial protection, for instance, tailoring the cardioplegia to the specific clinical situation (patients age, ventricular physiology, and ischemic risk), integration with organ preservation technologies that are been used for transplant, better biomarker assessment of myocardial injury during cardiac surgery, and refinement of cardioplegia solutions.

CONCLUSION

The evolution of cardioplegia reflects a progression from early crystalloid arrest to oxygenated blood-based protection and, more recently, to hybrid solutions such as del Nido. Pioneering work in warm blood cardioplegia and delivery strategies reshaped global practice. Myocardial protection continues to evolve with innovations in delivery, temperature management, and minimally invasive techniques.

Data Availability

The authors declare that the data supporting the findings of this study are available within the article.

Artificial Intelligence Usage

The authors declare the use of Copilot for English language review. The content produced by the artificial intelligence tool was revised and edited by the authors as necessary, and they take full responsibility for the content to be published.

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Potential Conflict of Interest

The authors declare that there is no conflict of interest in this study.

Authors' Roles & Responsibilities

TS	Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published
JRB	Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

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