

2023

Myocardial Protection in High-Risk Cardiopulmonary Bypass Support

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Recommended Citation

CHATTERJEE, SUBHASIS and Moon, Marc R. (2023) "Myocardial Protection in High-Risk Cardiopulmonary Bypass Support," *Journal of Shock and Hemodynamics*: Vol. 2(1) :E2023214 DOI: <https://doi.org/10.58464/2836-0605.1045>

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Myocardial Protection in High-Risk Cardiopulmonary Bypass Support

Cover Page Footnote

Stephen N. Palmer, PhD, ELS, of the Department of Scientific Publications at The Texas Heart Institute, contributed to the editing of the manuscript.

2023 Symposium Presentation**Myocardial Protection in High-Risk Cardiopulmonary Bypass Support****Subhasis Chatterjee, MD^{1,2,3}; Marc R. Moon, MD^{2,3}**¹Division of Trauma/Acute Care Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX²Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX³Department of Cardiovascular Surgery, The Texas Heart Institute, Houston, TX**Email:** subhasis.chatterjee@bcm.edu*Received September 14, 2023**Accepted October 15, 2023**Published December 11, 2023***Abstract**

The development of cardioplegia has facilitated complex cardiac surgery and allowed high-risk patients to safely tolerate life-saving procedures. By following the principles of electromechanical arrest, inducing hypothermia, and using adjunctive agents to help mitigate the effects of hypothermia and ischemia reperfusion injury, cardioplegia can be safely induced with various commercially available compositions, which can be delivered by several different surgical techniques. Although many studies have compared these methods, there is little consensus on whether any one method is superior to another. Just as a surgeon may need to modify technique according to individual patient factors, so too must a surgeon be flexible and be prepared to use different cardioplegia strategies according to the clinical circumstances. Increasing evidence shows the advantage of coronary artery bypass grafting (CABG) over percutaneous interventions in patients with low ejection fractions. Thus, optimal myocardial protection will continue to be necessary in this higher-risk cohort. Moreover, while patients in cardiogenic shock rarely present for CABG, the high mortality in this cohort demonstrates the need for ongoing efforts to improve myocardial protection. Lastly, there may be circumstances in which alternative approaches involving fibrillatory arrest or keeping the heart beating are more effective than conventional cardioplegia. These techniques should all be part of the surgeon's armamentarium, enabling the surgeon to tailor the operation to the individual patient.

Keywords: cardioplegia, myocardial protection, ischemia reperfusion injury**Background**

The advances in cardioplegia followed the progress in cardiac surgery during the mid-20th century. Cardioplegia is a therapy that stops the heart safely for more extended periods, thus facilitating complex intracardiac repair. During high-risk cardiac surgery, myocardial protection is critical to minimizing the risk of postoperative myocardial dysfunction and a low cardiac output state.

A high-risk case may involve a relatively straightforward operation in a critically ill patient or a very complex operation in a healthier, more stable patient. Five situations can be considered high risk: 1) acute myocardial infarction and

cardiogenic shock; 2) decreased left or right ventricular function or pulmonary hypertension; 3) an expected long operation with a prolonged myocardial ischemia time (eg, multiple valve surgery); 4) a re-operation with the risk of catastrophic hemorrhage and massive transfusions; and 5) a less complex operation in a patient with major noncardiac (neurologic, renal, hepatic, respiratory) comorbidities. With respect to myocardial protection, the first three situations are the most relevant.

Assuming that the multidisciplinary heart team has ruled out alternatives to surgery (transcatheter or percutaneous alternatives, delaying surgery for medical optimization, or avoiding surgery and considering palliation), several

preoperative and operative strategies may be employed.^{1,2} It is important to recognize that different approaches to cardioplegia exist, including conventional cardioplegia, the use of newer cardioplegia solutions, the “beating-heart” approach, which avoids cardioplegia altogether, and the no cardioplegia/no cardiopulmonary bypass (“off-pump”) approach. Furthermore, under the principle that “failing to prepare is preparing to fail,” it is important to consider adequate temporary mechanical circulatory support (MCS) options in the early perioperative period. Early initiation of MCS is preferable to prolonged periods of post-cardiotomy cardiogenic shock involving escalating vasoactive medications and end-organ malperfusion. In selected patients, preoperative evaluation by the durable MCS and heart transplant teams may be appropriate to determine patient eligibility in advance, should those therapies be needed. Finally, palliative care consultation may be appropriate for some patients before surgery to clearly delineate the wishes and expectations of the patient, family, and surgeon.

In this review, we examine the major developments in the history of cardioplegia, compare different cardioplegic solutions and their delivery methods, discuss strategies for using cardioplegia in high-risk patients, and explore alternatives to cardioplegia, where applicable.

Clinical Need

Increasing evidence demonstrates the superiority of coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) in patients with low left ventricular ejection fraction (LVEF). Sun and colleagues used the Ontario provincial database to identify 12 113 patients with an LVEF < 35% who were treated over 8 years.³ A total of 2397 propensity score–matched pairs were compared, with a primary outcome of all-cause mortality and a median follow-up of 5 years. Early (30-day) mortality was similar between the two groups (CABG 4.0% versus PCI 4.8%, $P = .21$); however, long-term mortality was lower with CABG (23.3%) than with PCI (30.0%; hazard ratio 1.6 [1.4-1.7], $P < .001$, number needed to treat [NNT] = 15).

Regarding cardiogenic shock, Acharya and colleagues analyzed the Society of Thoracic Surgeons Adult Cardiac Surgery Database and found that 1.5% of CABG procedures were for patients who presented with cardiogenic shock.⁴ The overall operative mortality in this cohort was 19%, with CABG under salvage conditions associated with a 53% mortality rate. Thus, patients with a low LVEF and those presenting with cardiogenic shock continue to be an important segment of the modern CABG population, so making the operation as safe as possible remains imperative.

Brief History of Myocardial Protection

Early attempts at valvular heart surgery often resulted in the dreaded “stone heart” caused by ischemic contracture.⁵ Overcoming this problem necessitated ongoing refinements in myocardial protection beyond simple aortic cross-clamping with ischemic preconditioning. In 1955, rapid cardiac arrest

with a high-potassium citrate solution was first reported by Melrose et al.⁶ Still, by the early 1960s, this strategy was nearly abandoned because of the considerable myocardial injury that patients sustained. In 1967, Reidemeister and Bretschneider induced cardiac arrest with intracellular sodium and calcium depletion,⁷ which led to the development of histidine-tryptophan-ketoglutarate (HTK) and Custodiol Solution (Essential Pharmaceuticals). It was not until the 1970s that Gay and Ebert resurrected potassium-based cardioplegia by reducing the potassium citrate concentration to widely tolerable levels.⁸ In 1977, Hearse and colleagues developed a crystalloid cardioplegia solution with high concentrations of magnesium and potassium; this mixture became known as the St. Thomas’ Hospital solution, also called Plegisol (Pfizer).⁹ Between 1978 and 1995, Buckberg introduced cold-blood cardioplegia,¹⁰ followed by Calafiore and colleagues’ introduction of warm-blood cardioplegia,¹¹ while Menasché et al. showed the effectiveness of retrograde cardioplegia.¹² Buckberg and Salerno then reported their results using a combination of antegrade and retrograde blood cardioplegia,¹³ representing our preferred approach in higher-risk cases (Table 1).

Myocardial Protection for High-Risk Cardiac Surgery

The three critical components of myocardial protection are electromechanical diastolic arrest, hypothermia, and supplemental protective measures to mitigate the effects of hypothermia and ischemia-reperfusion injury.¹⁴ Different approaches to conventional cardioplegia have typically focused on three critical questions: 1) blood versus crystalloid, 2) cold versus warm, and 3) antegrade versus retrograde delivery. Each technique has vocal proponents, but there is little consensus in the surgical community about which is best, suggesting that they are all similarly effective.

The advantages of using a blood-based (rather than a crystalloid-based) approach to cardioplegia include better oxygen delivery, better buffering capacity, normal oncotic pressure (thus causing less tissue edema), and free-radical scavenging potential. The disadvantages are that the blood can obscure the operative field and that hypothermia results in a leftward shift of the oxygen-hemoglobin dissociation curve, thereby reducing oxygen availability. With cold crystalloid cardioplegia, on the other hand, oxygen delivery is not affected by temperature, and the clear solution allows for good visualization of the operative field. These advantages come at the cost of more hemodilution, lower oncotic pressure, and more tissue edema.¹³

Two meta-analyses compared blood and crystalloid cardioplegia. Zeng and colleagues performed a meta-analysis of 12 studies involving 2866 patients and compared cold-blood cardioplegia with cold-crystalloid cardioplegia. They found that blood cardioplegia was associated with a slightly lower incidence of perioperative myocardial infarction (2.4% versus 1.2%; relative risk [RR] = 2.3; $P = .003$; NNT = 83). There was no difference between the two groups regarding the return to spontaneous sinus rhythm or the incidence of postoperative atrial fibrillation, stroke, or mortality.¹⁵

Table 1. Comparison of cardioplegia solutions most commonly used in modern practice ^a

	Histidine-Tryptophan-Ketoglutarate (HTK; Bretschneider's, Custodiol™)	St Thomas Solution, Plegisol™	Del Nido	Blood-based 4:1 induction (Buckberg)
	Crystalloid	Crystalloid	Crystalloid	Blood
Cellular	Intracellular	Extracellular	Extracellular	Extracellular
Electrolytes	Na ⁺ 15; K ⁺ 9; Mg ²⁺ 4, Ca ²⁺ 0.015	Na ⁺ 110; K ⁺ 16; Mg ²⁺ 16, Ca ²⁺ 1.2, HCO ³⁻ 10	Na ⁺ 140; K ⁺ 26; Mg ²⁺ 3; Cl ⁻ 98	Na ⁺ 140; K ⁺ 20; Mg ²⁺ 13
pH	7.02-7.20	7.8	7.4	7.2
Ingredients	<ul style="list-style-type: none"> • Histidine (buffer) • Tryptophan (membrane stabilizer) • Ketoglutarate (ATP) • Mannitol (osmotic, free radical scavenger) 	<ul style="list-style-type: none"> • Procaine HCl (membrane stabilizer with cardioplegic effects) 	<ul style="list-style-type: none"> • Lowers energy consumption, scavenges free radicals, • Lidocaine 130, reduces edema, promotes anaerobic glycolysis 	<ul style="list-style-type: none"> • Glucose • Lidocaine 260 • Tromethamine
Features	<ul style="list-style-type: none"> • Single cardioplegic dose so uninterrupted surgery • Longer time needed for arrest due to low K⁺ 	<ul style="list-style-type: none"> • Rapid arrest due to high K⁺ • Repeated dosing needed 	<ul style="list-style-type: none"> • Single cardioplegic dose so uninterrupted surgery • Lower cardioplegia volume needed 	<ul style="list-style-type: none"> • Better oxygen delivery and buffering capacity • Obscure operative fluid with continuous administration

^a Portions of this table are reprinted from *Perfusion*, 36, Whittaker A, Aboughdir M, Mahbub S, et al., "Myocardial protection in cardiac surgery: How limited are the options? A comprehensive literature review," 338-51, Copyright (2021), with permission from SAGE Publications

Guru et al. evaluated 34 studies comprising 5044 patients. They found a lower incidence of creatine kinase-myocardial band (CK-MB) release with blood cardioplegia than with crystalloid cardioplegia; however, they found no difference in the mortality or myocardial infarction rates.¹⁶

Table 1 compares various common cardioplegia solutions.¹³ The 2021 American Association for Thoracic Surgery Expert Consensus Document on CABG in Ischemic Cardiomyopathy and Heart Failure makes a Class I recommendation (Level of Evidence B-non-randomized) favoring blood over crystalloid cardioplegia.¹

With respect to temperature, cold (4°C) cardioplegia offers the advantages of lowering myocardial oxygen demand and enhancing oxygen delivery as a result of factors that promote oxygen unloading, such as local myocardial acidosis and hypercarbia; cold cardioplegia may also have neuroprotective properties. However, it comes with certain disadvantages, including the inhibition of myocardial enzymes and Na-K and Calcium-ATPase systems, increased myocardial edema from hemodilution, heightened risk of reperfusion injury, and a rightward shift of the oxyhemoglobin disassociation curve, resulting in lower oxygen availability. Warm (37°C) cardioplegia is associated with less ischemia-reperfusion injury when administered continuously. Nonetheless, it requires higher volumes of cardioplegia solution, leading to poorer visualization, an increased risk of hyperkalemia due to the higher potassium concentration, and a slightly greater likelihood of poor neurological outcomes.¹³ An alternative approach, tepid (28°C) cardioplegia, has also been used by some clinicians.¹⁷ An exhaustive systematic review of 46 studies, including 35 randomized trials with 15 248 patients, showed no major differences in clinical outcomes between cold and warm cardioplegia.¹⁸

Concerning delivery methods, the antegrade administration of cardioplegia solution through the aortic root is an effective way to induce cardiac arrest rapidly. However, this approach carries certain risks, including the heterogeneous distribution of the solution due to coronary occlusion and stenoses, coronary emboli in patients undergoing redo CABG, and coronary ostial injury. Additionally, antegrade delivery can be challenging in patients with aortic insufficiency or a Type A aortic dissection. In contrast, retrograde cardioplegia, delivered via the coronary sinus and into the cardiac veins, offers several advantages. It can be used in cases of coronary occlusion, is administered continuously without interrupting the surgical procedure, and can reduce the risk of embolization in redo CABG by flushing air and debris from the coronary arteries. However, retrograde cardioplegic arrest is slower, poses a potential risk of coronary sinus injury, and may not provide adequate myocardial protection of the right ventricle.¹⁹ The advantages of both techniques can be seen when a combined antegrade/retrograde approach is used.¹³ This technique may be particularly beneficial for patients with left ventricular hypertrophy.²⁰

Thus, while most surgeons have specific cardioplegia preferences based on their training and clinical experience, there are limited data supporting the superiority of any particular approach. Systematic reviews generally reveal heterogeneity among clinicians in their choice between continuous and intermittent administration, as well as in the use of a "hot-shot" or terminal dose of warm blood before aortic unclamping—variations that could potentially impact outcomes in certain patients.²¹ An astute surgeon maintains a degree of flexibility, recognizing that in specific clinical situations, one method of cardioplegia may offer a unique advantage that justifies its use.

Newer Approaches

“Newer” approaches to cardioplegia include del Nido cardioplegia (DNC), designed by del Nido at the University of Pittsburgh in the 1990s to address the vulnerability of an infant's heart to calcium overload and ischemia-reperfusion injury. The chief advantage of DNC lies in its intracellular ionic composition, as opposed to an extracellular ionic composition. Whereas conventional blood cardioplegia typically requires re-administration every 15-30 minutes, DNC can last for up to 60-75 minutes, significantly reducing the need for frequent re-administration.²²

A systematic review and meta-analysis of 29 studies involving 18 388 patients found that DNC is comparable in effectiveness to blood cardioplegia.²³ Cardiopulmonary bypass and myocardial ischemia times were similar between groups, but less defibrillation was required in the DNC group. Mortality was similar between groups in the overall cohort, the randomized trials, and a propensity-matched analysis. Additionally, rates of elevated troponin T levels, postoperative atrial fibrillation, and transfusion were similar between the two groups, while acute kidney injury occurred less frequently in the DNC cohort. In a propensity score-matched analysis of 88 patients who underwent CABG after acute myocardial infarction, DNC was not associated with low cardiac output syndrome.²⁴

Tan and colleagues performed a network-level meta-analysis by reviewing data from 18 randomized trials and 49 observational cohort studies, which included 18 191 adult and pediatric patients in 55 studies.²⁵ Among adult patients, the risk of mortality was significantly higher for the HTK (RR 1.89, 95% CI 1.10, 3.52) and blood cardioplegia groups (RR 1.73, 95% CI 1.22, 2.79) than for the DNC group. However, the risk of atrial fibrillation was significantly higher with DNC (RR 1.51, 95% CI 1.15, 2.03) and blood cardioplegia (RR 1.41, 95% CI 1.09, 1.86) than with HTK. Overall, it appears that the effectiveness of DNC is comparable to that of the standard cardioplegia formulations currently available. This single-shot approach has facilitated the use of minimally invasive surgery, causing less disruption in the procedure than conventional intermittent cardioplegia dosing (Table 1).²⁶

Because the standard formulation of blood cardioplegia is a 4:1 or 8:1 dilution with crystalloid, the rationale behind using whole-blood cardioplegia, also known as microplegia, is to reduce the crystalloid volume, which may benefit patients by minimizing hemodilution. This technique was analyzed in a review of 11 studies and 5798 patients. The microplegia cohort indeed had a lower crystalloid volume requirement, along with a higher frequency of spontaneous heart rate return, lower inotrope requirements, and lower CK-MB levels than patients receiving standard blood-based cardioplegia solutions.²⁷ Furthermore, microplegia was associated with a shorter ICU length of stay and similar mortality. Although these results are promising, large prospective randomized trials are necessary to establish the clinical superiority of microplegia over conventional cardioplegia, especially in higher-risk cases.

From a surgical standpoint, high-risk cases demand a high level of technical proficiency. Therefore, if a surgeon routinely uses beating-heart or off-pump coronary artery bypass (OPCAB) techniques, it is prudent to perform high-risk cases in that manner. Conversely, if a surgeon rarely uses these techniques, it is less likely that optimal outcomes will be achieved in a high-risk scenario.

In patients with acute myocardial infarction, surgeons can consider a combination of antegrade and retrograde cardioplegia and perfuse distal bypass grafts after completing the anastomosis. To ensure adequate cardioplegia delivery, a myocardial temperature probe can be used.²⁸ In some cases, left ventricular (LV) venting may be necessary to ensure proper LV decompression and optimal cardioplegia delivery. Finally, it is advisable to have a contingency plan in place, such as a salvage bailout strategy using MCS, should the need arise.

Table 2 outlines alternative techniques.¹ Some surgeons have adopted a technique known as beating-heart on-pump CABG, in which cardiopulmonary bypass is initiated, but the heart is not actually stopped. A review of 11 studies, including two randomized trials, showed a statistically significant survival benefit in five trials using this approach.²⁹ Interestingly, the patients who benefited most from beating-heart on-pump CABG included those with preoperative risk factors such as hemodialysis, end-stage coronary artery disease, emergency surgery, and a low LVEF.

As an alternative, some surgeons have used fibrillatory arrest during cardiopulmonary bypass to allow continuous myocardial perfusion with the heart in a motionless state.³⁰ This technique can also be selectively applied in re-operative cases to avoid aortic cross-clamping and to facilitate a non-sternotomy approach.

Lastly, for centers experienced with OPCAB, two large database analyses have shown favorable results in patients with an LVEF < 30%. Keeling and colleagues performed an intention-to-treat analysis comparing OPCAB with on-pump CABG using data from the STS Adult Cardiac Surgery Database from 2008-2011.³¹ Of these operations, 20.1% were performed with an OPCAB technique. Among patients with a low LVEF, the risk of operative mortality was lower in the OPCAB group (3% versus 6%, $P = .006$, OR = 0.82), but this was accompanied by reduced revascularization (2.9 versus 3.5 grafts, $P < .001$). Notably, 5.2% of OPCAB patients had unplanned conversions, resulting in a 9.3% mortality rate.

Similarly, Ueki et al. used data from the Japan Adult Cardiovascular Surgery Database from 2008-2012 to identify 2187 patients with a low LVEF. They analyzed 918 propensity score-matched pairs of CABG and OPCAB patients.³² The OPCAB group showed lower mortality (3% versus 6%, $P < .001$), with a volume-adjusted odds ratio of 0.5. As in Keeling et al.'s analysis, the 6% of OPCAB patients who needed conversion to CABG faced a higher risk of mortality than would be expected with planned CABG.

Table 2. Coronary artery bypass grafting strategies: features and applications^b

Strategy	Pros	Cons	Appropriate application
On-pump, cardioplegic arrest	<ul style="list-style-type: none"> Bloodless and still operative field Facilitates complete revascularization Hemodynamic stability 	<ul style="list-style-type: none"> Physiologic insult of cardiopulmonary bypass and associated morbidity (e.g., increased risk of bleeding and blood transfusion, atrial fibrillation) Global myocardial ischemia (blunted with meticulous myocardial protection) 	<ul style="list-style-type: none"> Default technique
Off-pump	<ul style="list-style-type: none"> Reduced perioperative morbidity 	<ul style="list-style-type: none"> Increased risk of incomplete revascularization Potential risk of reduced long-term survival High morbidity and mortality associated with conversions from off- to on-pump, particularly unplanned conversions Potential reduced graft patency 	<ul style="list-style-type: none"> Surgical expertise Hemodynamic stability Diseased ascending aorta
On-pump beating heart	<ul style="list-style-type: none"> Avoid ischemic arrest Preserve right ventricular perfusion 	<ul style="list-style-type: none"> Risk of watershed myocardial infarction. Especially with reduced perfusion pressures 	<ul style="list-style-type: none"> Surgical expertise Diseased ascending aorta (clamping contraindicated or associated with increased risk) May be helpful in patients with significant right ventricular dysfunction
Multiarterial grafting	<ul style="list-style-type: none"> Potential for improved long-term graft patency and improved longevity 	<ul style="list-style-type: none"> Risk of insufficient early conduit blood flow Risk of conduit spasm, particularly in patients on high doses of vasopressor support May prolong operative and myocardial ischemic time Insufficient conduit length in a dilated heart 	<ul style="list-style-type: none"> Surgical expertise Young patients with absence of severe non-cardiac comorbidities that can limit their survival Poor vein conduits Expected low postoperative vasopressor dose

^bReprinted from J Thorac Cardiovasc Surg, 162 (e1), Bakaeen FG, Gaudino M, Whitman G, et al., "The American Association for Thoracic Surgery Expert Consensus Document: Coronary artery bypass grafting in patients with ischemic cardiomyopathy and heart failure," 829-50, Copyright (2021), with permission from Elsevier

Current Approach to Cardioplegia

Two surveys conducted in recent years provide a broad perspective on current practices. In 2018, Ali and colleagues conducted a worldwide survey of 926 centers in Europe and North America, revealing that blood cardioplegia was used in approximately 60-80% of cases, while crystalloid was used in about 20% of cases.³³ In 2023, Lohbusch and coworkers received survey responses from perfusionists at 58 centers in the Eastern and Mid-Atlantic regions of the United States. Their findings indicated that DNC was used in roughly 62% of all cases, 48% of CABG cases, and 59% of non-CABG procedures.³⁴ Among the alternatives, a 4:1 solution was the most common (41-47%), followed by microplegia (24%). These results reflect the wide variation in practice patterns and the absence of a general consensus on optimal methods.

Summary

Myocardial protection remains a critical component of successful cardiac surgery. In the 1980s, myocardial protection was a major topic in this field, highlighting the remarkable progress cardiac surgery has made regarding safety. Today, optimal methods of myocardial protection are less hotly debated. Few randomized trials have unequivocally

demonstrated the superiority of one form of cardioplegia over another. Consequently, assigning proper endpoints in future trials may prove challenging, given varying definitions of myocardial injury or low cardiac output syndrome.

The adoption of single-dose del Nido and HTK-Custodiol solutions has increased. Surgeons should be familiar with different forms and techniques of delivery to tailor the optimal cardioplegia strategy for individual patients. Finally, the old adage that "failing to prepare is preparing to fail" is worth remembering, underscoring the importance of developing backup plans in advance.

How do These Concepts Impact Clinical Practice?

Various cardioplegia solutions and delivery methods with comparable efficacy are available. Surgeons should diligently employ myocardial protection and be proficient at using different techniques when clinically indicated. The increasing use of single-shot cardioplegia has enabled minimally invasive approaches. At times, alternatives to conventional cardioplegia are necessary.

Disclosures

Dr. Chatterjee has served on advisory boards for Edwards Lifesciences, La Jolla Pharmaceutical Company, Baxter Pharmaceuticals, and Eagle Pharmaceuticals, Inc. Dr Moon is a consultant/advisory board member for Medtronic and Edwards Lifesciences.

Funding

None.

Acknowledgment

Stephen N. Palmer, PhD, ELS, of the Department of Scientific Publications at The Texas Heart Institute, contributed to the editing of the manuscript.

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