*Original Article*

ASIAN CARDIOVASCULAR & THORACIC ANNALS

Asian Cardiovascular & Thoracic Annals
0(0) 1–7

DOI: 10.1177/0218492320966434
journals.sagepub.com/home/aan

SAGE

# Clinical outcomes of single-dose cardioplegia in high-risk coronary bypass

**Serdar Gunaydin[1], Orhan Eren Gunertem[1], Seyhan Babaroglu[1], Atike Tekeli Kunt[1], Kevin McCusker[2] and Kanat Ozisik[1]**



## Abstract

**Background:** Despite the increasing popularity of single-dose cardioplegia techniques in coronary artery bypass grafting, the time window for successful reperfusion remains unclear. This study aimed to compare different cardioplegic techniques based on early and 30-day clinical outcomes via thorough monitoring.

**Methods:** This prospective cohort study included high-risk patients undergoing coronary artery bypass grafting and receiving 3 different types of cardioplegia between January 2017 and June 2019. Group 1 ($n = 101$) had a single dose of del Nido cardioplegia, group 2 ($n = 92$) had a single dose of histidine-tryptophane-ketoglutarate, and group 3 ($n = 119$) had cold blood cardioplegia. Patients were examined perioperatively by memory loop recording and auto-triggered memory loop recording for 30 days, with documentation of predefined events.

**Results:** Interleukin-6 and cardiac troponin levels in group 1 were significantly higher than those in groups 2 and 3. The incidence of predefined events as markers of inadequate myocardial protection was significantly higher group 1, with more frequent atrial fibrillation attacks and more hospital readmissions. The readmission rate was 17.6% in group 1, 9% in group 2, and 8% in group 3.

**Conclusions:** Our data demonstrate the long-term efficacy of cardioplegic techniques, which may become more crucial in high-risk patients who genuinely have a chance to benefit from adjunct myocardial protection. Patients given del Nido cardioplegia had a significantly more prominent inflammatory response and higher troponin levels after cardiopulmonary bypass. This group had issues in the longer term with significantly more cardiac events and a higher rehospitalization rate.

## Keywords

Cardioplegic solutions, coronary artery bypass, heart arrest, induced

## Introduction

Myocardial preservation includes the methods used during the operation to prevent ischemia-reperfusion injury. These techniques help lower metabolic activity and minimize stunning and perioperative cell destruction.[1] There is still no evidence-based data, especially real-time indicators, for the evaluation of protection. Many publications have documented clinical outcomes based on indirect parameters such as electrocardiogram changes, atrial fibrillation, echocardiography, low cardiac output, inotropic support, intraaortic balloon pump insertion, and the duration of intensive care unit stay. These parameters may be affected by other factors including surgery and anesthesia, and it is difficult to understand the role played by each factor.[2,3] In particular, outcomes related to long-term follow-up have not been studied in detail. The effects of myocardial preservation methods on the inflammatory process have been well documented.[4] The inflammatory response correlates with the degree of endothelial injury, and this may give an estimation of protection.

[1]Department of Cardiovascular Surgery, City Hospital Campus, University of Health Sciences, Ankara, Turkey
[2]Department of Cardiac Surgery, New York Medical College, New York, USA

**Corresponding author:**
Serdar Gunaydin, Faculty, Department of Cardiovascular Surgery, City Hospital Campus, Ankara, Turkey.
Email: serdarkvc@gmail.com

Cold blood potassium-based cardioplegia (BC) in a 4:1 (blood: crystalloid) solution has been proven to be better than crystalloid-based formulations. The beneficial effects of BC include the oncotic features of blood, buffering power, creation of an oxygen-rich medium, intermittent reoxygenation, and washout of metabolites, with no need for substrate (glucose and insulin).[5] The dilemma over the best re-dosing timing has not been solved, but while multiple-dose cardioplegia has been the gold standard for decades, single-shot cardioplegia is becoming more popular as a valuable alternative. Histidine-tryptophane-ketoglutarate (HTK; Custodiol, Bensheim, Germany) is an intracellular crystalloid solution with low concentrations of sodium and calcium ions. Sodium becomes depleted in the extracellular space, resulting in hyperpolarization of the myocytes, which induces cardiac arrest in diastole. Histidine is an important buffer for anaerobic acidosis, ketoglutarate implements adenosine triphosphate production during reperfusion, and tryptophan is a stabilizer of the cell membrane. Mannitol reduces edema and also acts as a free-radical scavenger.[6,7] del Nido cardioplegia (DNC) has been used for more than 20 years in pediatric practice in a single-dose fashion. Lately, it has been introduced into adult surgery, triggering a growing interest. Current literature in adult and pediatric patients confirms that it is safe and a good alternative to conventional techniques.[8,9]

Single-dose perfusion techniques have become more popular in adult cardiac surgery recently, including coronary artery bypass grafting (CABG). With encouraging experimental data and verified safe use in the pediatric population, these solutions provide extended myocardial arrest and reduce damage through better protection of the intracellular contents.[10,11] Many published studies have investigated the use of single-dose techniques only under the most preferable conditions in patients with limited comorbidities undergoing elective surgery.[12,13] Comparative publications based on propensity matching in conventional cardioplegia versus a single-dose strategy in CABG, valve surgery, and reoperations have presented similar postoperative results. These reports showed that the use of single-dose cardioplegia resulted in fewer infusions, shorter aortic crossclamp times, and better glucose patterns. No differences have been demonstrated in ischemia markers or the incidence of low cardiac output or major complications.[14,15]

We consider that mortality in the general population or in the low-risk population is not a suitable endpoint because there is little room for improvement. It would be a proper endpoint in studies with high-risk patients because mortality is higher. Also, the impact of myocardial preservation on inflammation has been well investigated. Based on data supporting that the inflammatory response correlates with the degree of endothelial injury, interleukin-6 levels were also measured in this study to project endothelial function. The target is not just to get to the shore, but also to use the best, simplest, fastest, and most the cost-effective technique to reach the optimal results. Therefore, we designed a study to compare the most popular single-dose techniques with BC in high-risk patients undergoing CABG, including through one-month follow-up.

## Patients and methods

The Institutional Ethics Committee approved this study (Ministry of Health, Numune Training & Research Hospital Ethics Committee for Clinical Studies. Issue no: 18-2307). Patients' informed consent forms were collected in all cases. From January 2017 until June 2019, 312 high-risk patients (Society of Thoracic Surgeons risk score >8%) who underwent CABG in our institution were prospectively randomized into 3 groups based on the type of cardioplegia used, and their data were collected. The composition of each cardioplegic solution is shown in Table 1.

All patients received the calculated dose under controlled pressure within the predefined duration. The DNC group was 101 patients given single-dose DNC (2/3 antegrade + 1/3 retrograde) at 4–8°C, 20 $mL \cdot kg^{-1}$ in 5 min, at 80–100 mm Hg pressure (<30 mm Hg retrograde). The HTK group was 92 patients given single-dose HTK cardioplegia (2/3 antegrade + 1/3 retrograde) at 4–8°C, 20 $mL \cdot kg^{-1}$ in 7 min, at 80–100 mm Hg pressure (<30 mm Hg retrograde). The BC group was the control group of 119 patients given cold BC 4:1 (2/3 antegrade + 1/3 retrograde) at 4–8°C every 25 min, with an initial dose of 15 $mL \cdot kg^{-1}$ in 5 min, at 80–100 mm Hg pressure, followed by half doses (<30 mm Hg retrograde). We always utilize antegrade + retrograde perfusion for single-dose cardioplegia, especially because the target protection time is around 90 min. Considering the coronary artery lesions, including the right coronary artery, antegrade + retrograde perfusion theoretically provides complete distribution over the heart, and is the safest option.

The randomization started before enrollment on the night before surgery, via sealed consecutively numbered envelopes, by a blinded member of the study team. Inclusion criteria were adult patients aged 50 to 79 years, those providing informed consent, and patients scheduled for CABG requiring cardiopulmonary bypass (CPB) and myocardial arrest with aortic crossclamp time expected to be <90 min. Exclusion criteria were severe hemodynamic instability requiring high doses of inotropic drugs, patients with an implanted pacemaker or cardioverter-defibrillator, severe heart failure (New York Heart Association

**Table 1.** Composition of the cardioplegic solutions used.

| Cardioplegia solution | Contents |
|---|---|
| del Nido | Base solution (mmol·L$^{-1}$): $Na^{+}$ 140, $K^{+}$ 5, $Mg^{++}$ 3<br>$K^{+}$ 7.5% 26 mL<br>Mannitol 20% 16.3 mL<br>$Mg^{++}$ 50% 4 mL<br>$HCO_3$ 8.4%: 13 mL<br>Lidocaine 1% 13 mL |
| Histidine-tryptophane-ketoglutarate | $Na^{+}$15 mmol·L$^{-1}$<br>$K^{+}$ 9 mmol·L$^{-1}$<br>$Mg^{++}$ 4 mmol·L$^{-1}$<br>$Ca^{++}$ 0.015 mmol·L$^{-1}$<br>Histidine 198 mmol·L$^{-1}$<br>Tryptophan 2 mmol·L$^{-1}$<br>Mannitol 30 mmol·L$^{-1}$ |
| Blood | Base: St. Thomas' Hospital solution<br>$K^{+}$ 40 mmol·L$^{-1}$<br>$NaHCO_3$ 10 mmol·L$^{-1}$<br>Mannitol 10 mmol·L$^{-1}$<br>Mixed with blood (4:1) |

**Table 2.** Preoperative characteristics of patients undergoing coronary artery bypass grafting with different types of cardioplegia.

| Variable | DNC group | HTK group | BC group |
|---|---|---|---|
| No. of patients | 94 | 88 | 107 |
| Age (years) | 71 ± 8 | 68 ± 10 | 73 ± 10 |
| Male | 61 | 56 | 72 |
| Body mass index (kg·m$^{-2}$) | 1.8 ± 0.5 | 1.76 ± 0.6 | 1.83 ± 0.6 |
| STS score | 10.1% ± 2% | 9.4% ± 1.3% | 10.1% ± 2% |
| LVEF | 43.6% ± 10% | 42.9% ± 10% | 48.1% ± 10% |
| History of AF | 10 | 8 | 12 |
| Associated disorders* | 83/72/54 | 70/64/48 | 92/80/57 |
| Serum creatinine (mg·dL$^{-1}$) | 1.1 ± 0.2 | 0.9 ± 0.3 | 1.0 ± 0.3 |

*Hypertension/diabetes mellitus/chronic obstructive pulmonary disease. AF: atrial fibrillation; BC: blood cardioplegia; DNC: del Nido cardioplegia; HTK: histidine-tryptophane-ketoglutarate; LVEF: left ventricular ejection fraction; STS: Society of Thoracic Surgeons.

class IV), ejection fraction < 30%, severe renal failure on dialysis or severe hepatic disease, anemia or a bleeding disorder (preoperative hematocrit < 20%), previous cardiac surgery, emergency surgery, severe pulmonary hypertension, and history of stroke or significant neurological dysfunction. Patients unable to be placed on retrograde cardioplegia and those needing re-dosing in the single-dose cardioplegia groups (aortic crossclamp time >90 min) were excluded. Data of patients in the BC group with aortic crossclamp times >100 min were also excluded. Preoperative data of the 3 groups are shown in Table 2.

The sample size was determined based on a similar study on single-dose cardioplegia.[16] Using the protocol, 65 patients were needed in each group to show a statistically significant difference with 5% error and 80% power. Giving an allowance for attrition and incomplete data of patients during follow-up, a sample size of 90 was targeted in each group. The primary outcomes included troponin I/inflammatory response as well as hospital and one-month follow-up complications. The secondary outcomes were the frequency of significant cardiac events recorded within one month postoperatively.

Anesthesia was induced with fentanyl 35 μg·kg$^{-1}$ (Talinat, Vem Pharma, Turkey), and muscle relaxation with pancuronium 0.1 mg·kg$^{-1}$ (Pavulon, MSD, Turkey). All patients received 3 mg·kg$^{-1}$ heparin (Roche, Turkey). Activated clotting time was measured using a Hemochron 801 (International Technidyne Corporation, Edison, NJ, USA) and maintained at greater than 480 seconds. Moderate hypothermia was induced at 32°C. After crossclamping the aorta, the heart was arrested using cardioplegia. Surface cooling

was employed. A complete anatomical revascularization strategy was preferred in each patient. The left internal mammary artery was used as a graft for left anterior descending artery bypass, and autologous saphenous vein grafts were routinely harvested for the other anastomoses. Proximal anastomoses were made under aortic crossclamping. Rewarming was initiated during the last proximal saphenous vein grafting. When 36.5°C and stable hemodynamics were reached, CPB was discontinued, and heparin was reversed with 3.1 mg·kg$^{-1}$ of protamine sulphate (Roche, Turkey) after decannulation.

CPB was instituted via arterial and venous cannulas (DLP, Minneapolis, MN) attached to coated tubing and a hollow-fiber oxygenator with an integrated arterial filter (Inspire 6 Phisio-coated, Livanova, Italy). Venous blood was drained by gravity into a hard-shell venous reservoir (Inspire, Livanova, Italy). The circuit was primed with 1200 mL (with a 200 mL safety margin in the reservoir) of Plasma-Lyte A. Retrograde autologous priming was performed in all groups. Mean arterial pressure was maintained between 50 and 70 mm Hg, and CPB flow was kept at 2.2–2.5 L·min$^{-1}$·m$^{-2}$. Red blood cell transfusion was used when the hematocrit was less than 21% during the perioperative period. In older patients (>70-years old), a hematocrit < 24% was accepted as the lowest limit. Platelet transfusion and fresh frozen plasma were used in a limited manner in all groups. All operations were performed by two surgeons (SG, KO).

Left atrial venting was applied in every case and started immediately after the initiation of CPB. To overcome hemodilution due to the acute volume infusion of approximately 2000 mL in a few minutes, venting started simultaneously with cardioplegia delivery. A retrograde cannula was placed, delivering 1/3 of the initial dose. The BC dose was repeated every 25 min via a retrograde cannula. The conventional DNC formula was used. For both single-dose techniques, a 90 min ischemic time was targeted. Patients needing re-dosing were excluded. Ultrafiltration was employed at the end of CPB in every group until a hematocrit of 25% was reached.

Complete blood count, prothrombin time, activated partial thromboplastin time, and fibrinogen level were recorded. Results of standard blood and urine chemistry were documented. Serum interleukin-6 and cardiac troponin levels were measured by enzyme-linked immunosorbent assay (Bender Medsystems, Vienna, Austria; coefficient of variation 10%, and sensitivity 1.4 pg·mL$^{-1}$). Blood samples were collected in potassium-ethylene diamine tetraacetic acid tubes at the following time intervals: baseline: after induction of anesthesia before CPB via retrograde cannula (T1); after cessation of CPB via the retrograde cannula (T2); and in the intensive care unit on the first postoperative day at 8 am (T3) via a radial artery.

The following factors were evaluated before discharge and at 1 week and 4 weeks postoperatively: hemodynamic variables, operative data, postoperative bleeding, use of blood/blood products, incidents of arrhythmia, use of inotropic support, complications and infection, duration of intensive care unit stay and hospital stay, perioperative mortality, New York Heart Association functional class, and Doppler echocardiography.

Patients were monitored (LifeStar ACT III, Malvern, PA, USA) via memory loop recording (MLR), and auto-triggered MLR (AT-MLR) on discharge up to the postoperative first month. LifeStar ACT III is a 3-channel ambulatory cardiac telemetry device that can function continuously for one month. The device automatically detects atrial fibrillation, tachycardia, bradycardia, and pauses. The clinician can get a daily summary and end of session reports on heart rate and blood pressure monitorization analysis, atrial fibrillation analysis (atrial fibrillation burden), arrhythmia classification and analysis, and extended electrocardiogram analysis surrounding any episode, upon request. Patients can manually transmit events by landline telephone and an emergency button on the device, to clinicians for analysis 24/7.

Postoperative symptoms demonstrating inappropriate myocardial protection were predefined by the study group: detailed analysis of QT intervals, ST segments, and heart rate variability; transient heart block, pauses, or ectopic rhythm; bradycardia (<50 beats·min$^{-1}$); tachycardia (>120 beats·min$^{-1}$); atrial fibrillation/flutter; severe angina; and readmission. The symptomatic and asymptomatic events that were documented, including those that met the predefined immediate physician notification criteria, and the times to first notification were compared.

Data are expressed as the mean ± standard error of the mean. Two-way analysis of variance was used to analyze differences over time in each group (repeated measures analysis of variance) and differences between groups. A $p$ value < 0.05 was considered significant. Data were analyzed using IBM SPSS version 22.0 for Windows (SPSS, Inc., Chicago, IL, USA).

## Results

A retrograde cannula could not be placed in 9 patients (2 each in the DNC and HTK groups and 5 in the BC group), 12 patients needed re-dosing (9 in the DNC group and 3 in the HTK group), and 7 patients in the BC group had a crossclamp time >100 min; all were excluded from the analysis. In the one-month follow-up, complete data could be obtained in 51

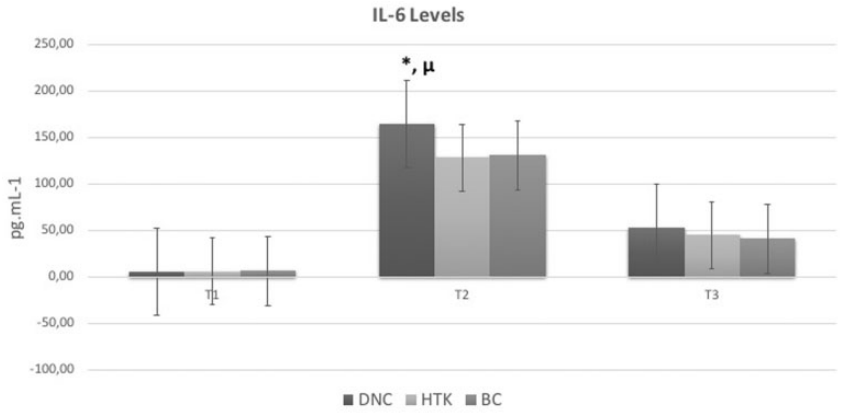


**Figure 1.** Interleukin-6 levels throughout the procedure. *$p < 0.05$ vs. group 3 (control). μ: $p < 0.05$ vs. group 2. BC: blood cardioplegia; DNC: del Nido cardioplegia; HTK: histidine-tryptophane-ketoglutarate; T1: after induction of anesthesia; T2: after cessation of cardiopulmonary bypass; T3: in the intensive care unit at 8 am on the first postoperative day.

**Table 3.** Early outcomes of coronary artery bypass grafting with different types of cardioplegia.

| Variable | DNC group | HTK group | BC group | *p* value |
|---|---|---|---|---|
| 3-vessel CABG | 70 | 63 | 77 | >0.05 |
| 4-vessel CABG | 24 | 25 | 30 | >0.05 |
| Aortic crossclamp time (min) | 81 ± 9 | 79 ± 8 | 82 ± 8 | >0.05 |
| Troponin I at T2 ($ng \cdot mL^{-1}$) | 9.11 ± 0.5* | 7.0 ± 0.5 | 6.35 ± 0.5 | 0.027 |
| IABP insertion | 8 | 5 | 5 | >0.05 |
| Hemorrhage (mL/24 h) | 750 ± 50 | 850 ± 50 | 650 ± 50 | >0.05 |
| RBC transfusion | 1.5 ± 0.5 | 1.6 ± 0.5 | 1.1 ± 0.5 | >0.05 |
| FFP transfusion | 2.6 ± 0.8 | 2.5 ± 0.7 | 2.2 ± 0.5 | >0.05 |
| Respiratory support (h) | 9.6 ± 3 | 8.4 ± 3 | 10.1 ± 4 | >0.05 |
| Cardioplegia volume (mL) | 1850 ± 50* | 1950 ± 50* | 2950 ± 100 | 0.035 |
| Ultrafiltration (mL) | 950 ± 250 | 1100 ± 250 | 1300 ± 250 | >0.05 |
| Atrial fibrillation† | 8/4 | 4/0 | 6/1 | >0.05 |
| LVEF before discharge | 41.2% ± 5% | 39.9% ± 5% | 40.1% ± 5% | >0.05 |
| ICU stay (days) | 1.8 ± 0.5 | 1.4 ± 0.5 | 1.4 ± 0.5 | >0.05 |
| Hospital stay (days) | 6.2 ± 1 | 5.6 ± 1 | 6.1 ± 1 | >0.05 |
| Hospital mortality | 1 | 0 | 1 | >0.05 |

*$p < 0.05$ versus group 3. †Non-permanent/permanent. CABG: coronary artery bypass grafting; BC: blood cardioplegia; DNC: del Nido cardioplegia; FFP: fresh frozen plasma; HTK: histidine-tryptophane-ketoglutarate; IABP: intraaortic balloon pump; ICU: intensive care unit; LVEF: left ventricular ejection fraction; RBC: packed red blood cells; T2: at the end of cardiopulmonary bypass.

patients in the DNC group, 44 in the HTK group, and 62 in the BC group, with an overall rate of 54.3%. No intervention for serum sodium levels nor any particular glucose strategy was necessary. Preoperative patient characteristics, routine blood chemistry, and complete blood counts at T1, T2, and T3 were not significantly different among the 3 groups. Serum cardiac troponin I levels did not show a significant difference among the 3 groups at baseline (T1) and T3. T1: 0.71 ± 0.1 in the DNC group, 0.66 ± 0.1 in the HTK group, and 0.46 ± 0.08 $ng \cdot mL^{-1}$ in the BC group. The levels dropped to 8.1 ± 0.5, 6.9 ± 0.4, 5.7 ± 0.5 $ng \cdot mL^{-1}$, respectively, at T3. At T2, troponin I levels in the DNC group were significantly higher than in the BC group. Interleukin-6 levels in the DNC group were significantly higher than in the HTK and BC groups at T2 (Figure 1). Early perioperative data are summarized in Table 3. Follow-up by MLR and AT-MLR on discharge up to the first postoperative month is summarized in Figure 2. All events were handled by an experienced clinician as soon as detected via telecommunication, employing urgent medical treatment. Any patient with a permanent or emergency event resistant to medical treatment was referred to the nearest hospital or our center, and readmitted. The frequency of monitored events was significantly more in the DNC group due to more atrial fibrillation and more readmitted patients. The readmission rate was 17.6% in the DNC group, 9% in the HTK group, and 8% in the BC group. Three patients in the DNC group, 2 in

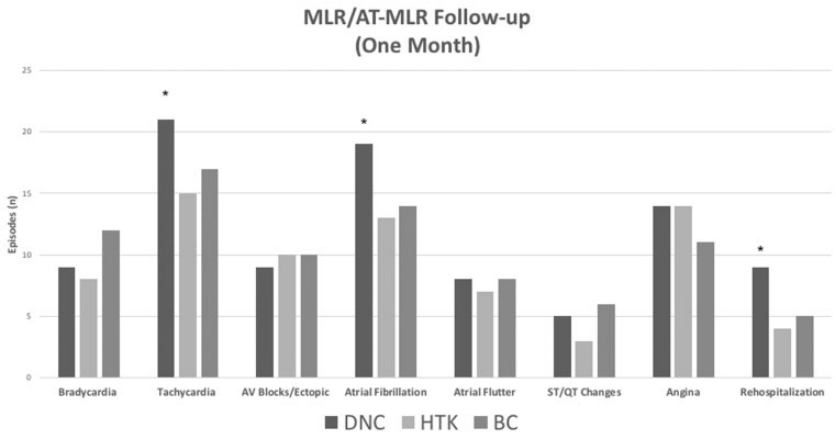


**Figure 2.** Longer-term follow-up by memory loop recording (MLR) and auto-triggered MLR (AT-MLR) on discharge up to the first postoperative month. $*p < 0.05$ vs. group 3 (control). BC: blood cardioplegia; DNC: del Nido cardioplegia; HTK: histidine-tryptophane-ketoglutarate.

the HTK group, and 3 in the BC group underwent coronary angiography; one patient each in the DNC and HTK groups received a percutaneous intervention. No reoperation was needed in any group.

## Discussion

There is growing interest in the different types of cardioplegia, but the endpoints and results have been completely different. The concerns may be due to the difficulties in standardization and fixing parameters for clear comparison.[17] There are, however, unanswered questions. The most critical problem is the definition of del Nido solution. There have been more than 300 formula variations introduced under the same name with definitely different chemical compositions. The safe duration of myocardial protection with DNC is also unclear. In pediatric cardiac surgery, publications cite over 2 h of ischemic time. We know that in valve surgery and especially pediatric surgery, the patient is cooled to a lower degree without retrograde cannulation. In CABG, the patient is much warmer, and even the distribution of antegrade cardioplegic solution has not been verified. Most clinics started with a 90-min safe ischemic time in early publications, but this was adjusted to 60 min in later reports.[17,18] In this study, attention was focused on surface cooling but the temperature could not be measured. This study aimed to assess the classic del Nido solution with 90 min ischemic time. For safety, a retrograde cannula was used in every case. Left atrial venting was also employed to exclude initial acute volume overload. Ion imbalance and further volume excess were handled by ultrafiltration at the end of CPB. Aortic crossclamp time was not different among the 3 groups because the proximal anastomoses were performed on crossclamp.

This study aimed to include additional sensitive parameters to give a broader comparison. Interleukin-6 and cardiac troponin I levels were significantly higher in the DNC group at the end of CPB. This may explain the poorer longer-term clinical outcomes. One-month follow-up is an additional aspect of this study. Most studies have given in-hospital comparisons with no difference in results. We defined criteria highly likely to be signs of inadequate myocardial protection in the longer term, and evaluated data of detailed monitoring. These signs might not be related only to cardioplegia but may result from many factors related to the whole process, however, they at least give a picture of the 1st postoperative month. Our follow-up was complete in 55% of patients, which is not entirely satisfactory but close to the target if you consider the difficulty in close monitoring.

One-month monitoring demonstrated more frequent arrhythmic events and a related readmission rate in the DNC group. A total of 18 readmissions were recorded; 8 patients were readmitted due to significant angina with electrocardiogram changes resistant to medical treatment: 3 in the DNC group, 2 in the HTK group, and 3 in the BC group underwent coronary angiography. Five patients in the DNC group, 2 in the HTK group, and 2 in the BC group were readmitted due to atrial fibrillation resistant to medical treatment. One patient in the DNC group was rehospitalized due to severe atrioventricular block.

The main limitation was that this was a single-center study with a relatively small population and a lack of the balancing impact of unmeasured confounders. Larger multicenter randomized clinical trials would

give a clearer idea. However, we concluded that cardioplegia selection should rely more on better scientific research, using evidence-based medicine and ranking of clinical studies rather than clinician's preference as the primary determining factor. Our data underline the importance of the long-term efficacy of cardioplegic techniques, which becomes more prominent in high-risk patients who genuinely have a chance to benefit from adjunct protection. DNC with a target ischemic time of 90 min has issues documented by an excessive inflammatory response and troponin I levels after CPB as well as longer-term protection with a more significant number of cardiac events and rehospitalization.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iD

Serdar Gunaydin https://orcid.org/0000-0002-9717-9793

## References

1. Ali JM, Miles LF, Abu-Omar Y, Galhardo C and Falter F. Global cardioplegia practices: results from the global cardiopulmonary bypass survey. *J Extra Corpor Technol* 2018; 50:83–93.
2. Hoyer A, Kiefer P and Borger M. Cardioplegia and myocardial protection: time for a reassessment? *J Thorac Dis* 2019;11:E76–E78.
3. Kuhn EW, Liakopoulos O, Slottosch I, et al. Buckberg versus Calafiore cardioplegia in patients with acute coronary syndromes. *Thorac Cardiovasc Surg* 2018; 66: 457–463.
4. Pouard P and Bojan M. Neonatal cardiopulmonary bypass. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2013; 16: 59–61.
5. Jacob S, Kallikourdis A, Sellke F and Dunning J. Is blood cardioplegia superior to crystalloid cardioplegia? *Interact Cardiovasc Thorac Surg* 2008; 7: 491–498.
6. Bretschneider HJ, Hubner G, Knoll D, Lohr B, Nordbeck H and Spieckermann PG. Myocardial resistance and tolerance to ischemia: physiological and biochemical basis. *J Cardiovasc Surg (Torino)* 1975; 16: 241–260.
7. Hummel BW, Buss RW, DiGiorgi PL, et al. Myocardial protection and financial considerations of Custodiol cardioplegia in minimally invasive and open valve surgery. *Innovations (Phila)* 2016;11:420–424.
8. Matte GS and del Nido PJ. History and use of del Nido cardioplegia solution at Boston Children's Hospital. *J Extra Corpor Technol* 2012; 44: 98–103.
9. Talwar S, Bhoje A, Sreenivas V, et al. Comparison of del Nido and St Thomas cardioplegia solutions in pediatric patients: a prospective randomized clinical trial. *Semin Thorac Cardiovasc Surg* 2017; 29: 366–374.
10. Chen Y, Liu J, Li S, Li W, Yan F, Sun P, Wang H and Long C. Which is the better option during neonatal cardiopulmonary bypass: HTK solution or cold blood cardioplegia? *ASAIO J* 2013; 59: 69–74.
11. Kalogeris T, Baines CP, Krenz M and Korthuis RJ. Cell biology of ischemia/reperfusion injury. *Int Rev Cell Mol Biol* 2012;298:229–317.
12. Guajardo Salinas GE, Nutt R and Rodriguez-Araujo G. Del Nido cardioplegia in low risk adults undergoing first time coronary artery bypass surgery. *Perfusion* 2017; 32: 68–73.
13. Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM and Fitzgerald D. The use of del Nido cardioplegia in adult cardiac surgery: a prospective randomized trial. *J Thorac Cardiovasc Surg* 2018;155:1011–1018.
14. Spellman J. Pro: in favor of more generalized use of del Nido cardioplegia in adult patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2019; 33: 1785–1790.
15. Siddiqi S, Blackstone EH and Bakaeen FG. Bretschneider and del Nido solutions: are they safe for coronary artery bypass grafting? if so, how should we use them? *J Card Surg* 2018;33:229–234.
16. Talwar S, Chatterjee S, Sreenivas V, et al. Comparison of del Nido and histidine-tryptophan-ketoglutarate cardioplegia solutions in pediatric patients undergoing open heart surgery: A prospective randomized clinical trial. *J Thorac Cardiovasc Surg* 2019; 157: 1182–1192. Available at: https://www.jtcvs.org/article/S0022-5223(18)33139-8/pdf.
17. An KR, Rahman IA, Tam DY, et al. A systematic review and meta-analysis of del Nido versus conventional cardioplegia in adult cardiac surgery. *Innovations (Phila)* 2019; 14: 385–393.
18. Stammers AH, Tesdahl EA, Mongero LB, Stasko AJ and Weinstein S. Does the type of cardioplegic technique influence hemodilution and transfusion requirements in adult patients undergoing cardiac surgery? *J Extra Corpor Technol* 2017; 49: 231–240.