Del Nido cardioplegia in isolated adult coronary artery bypass surgery

Tomasz A. Timek, MD, PhD,[a,b] Tyler Beute, BS,[b] Justin A. Robinson, BS,[b] Daniel Zalizadeh, MD,[b] Regina Mater, MD,[b] Jessica L. Parker, MS,[c] Matthew Lypka, MPH,[c] and Charles L. Willekes, MD[a,b]

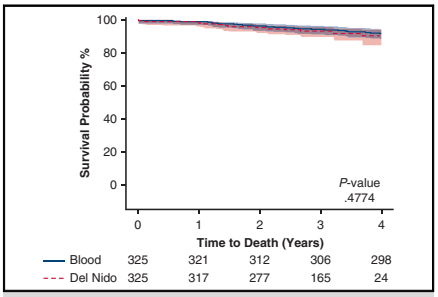
ABSTRACT

Background: Del Nido cardioplegia (DC) offers prolonged single-dose myocardial protection in pediatric cardiac surgery. We set out to evaluate the efficacy of DC in adult patients undergoing isolated coronary artery bypass grafting (CABG).

Methods: From January 2012 to October 2017, 851 consecutive isolated CABG surgeries were performed by 2 study surgeons at our center with blood cardioplegia (BC, n = 350), used from January 2012 to April 2014, and DC (n = 501), used from May 2014 to October 2017. Propensity matching was used to yield 325 well-matched pairs. Clinical data were extracted from our local Society of Thoracic Surgeons database and mortality data from the Michigan State Social Security Death Index.

Results: Single-dose administration was used in 83% (417/501) of patients receiving DC. In propensity-matched groups, postoperative median troponin T levels (0.28 [0.16-0.59] ng/mL vs 0.46 [0.27-0.81] ng/mL; $P < .01$) were lower for patients receiving DC, and no difference in ejection fraction on postoperative echocardiography was observed (54 ± 12% and 53 ± 13% for BC and DC, respectively; $P = .36$). Perioperative outcomes were similar except for greater rate of atrial fibrillation (33% vs 23%; $P = .01$) in the DC group. Subgroup analyses revealed equivalent myocardial protection and clinical outcomes in patients with age ≥75 years, left ventricular ejection fraction ≤35%, left main disease, or Society of Thoracic Surgeons score ≥2.5%. Four-year survival did not differ between patients undergoing BC or DC.

Conclusions: The current study revealed noninferior myocardial protection and clinical outcomes with DC versus BC in both routine and greater-risk patients undergoing isolated CABG. DC demonstrated the feasibility of single-dose administration for isolated CABG surgery. Larger randomized studies are needed to further explore the safety and efficacy of DC in adult cardiac surgery with longer crossclamp times. (J Thorac Cardiovasc Surg 2020;160:1479-85)



Propensity-matched data Kaplan–Meier survival curves for del Nido and blood cardioplegia in isolated adult coronary artery bypass surgery. *Shaded areas* represent confidence limits.

Central Message

Del Nido cardioplegia provided noninferior myocardial protection and clinical outcomes to blood cardioplegia in routine and greater-risk isolated coronary artery bypass patients with relatively short aortic crossclamp times.

Perspective

Optimal myocardial protection for cardiac surgical procedures continues to be debated. Del Nido cardioplegia has shown safety and efficacy in pediatric cardiac procedures, and current data confirm noninferior myocardial protection and clinical outcomes to blood cardioplegia in adult isolated coronary artery bypass surgery. Single-dose administration was sufficient for most patients undergoing CABG.

See Commentaries on pages 1486 and 1488.

Optimal myocardial protection for cardiac surgical procedures continues to be debated, yet clear superiority of a single cardioplegic solution remains to be established.[1] Similar to our institution, most centers in the United States use blood

Scanning this QR code will take you to the article title page to access supplementary information.

From the [a]Division of Cardiothoracic Surgery and [c]Office of Research, Spectrum Health, and [b]Michigan State University College of Human Medicine, Grand Rapids, Mich.

Internal institutional funds were used to support this study and no conflict of interest is associated with this investigation.

Received for publication Dec 19, 2018; revisions received Aug 14, 2019; accepted for publication Sept 6, 2019; available ahead of print Sept 24, 2019.

Address for reprints: Tomasz A. Timek, MD, PhD, Division of Cardiothoracic Surgery, Meijer Heart and Vascular Institute at Spectrum Health, Grand Rapids, MI 49506 (E-mail: Tomasz.Timek@specctrumhealth.org).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.09.027

Abbreviations and Acronyms

BC = blood cardioplegia
CABG = coronary artery bypass grafting
DC = Del Nido cardioplegia
LVEF = left ventricular ejection fraction
LV = left ventricular
STS = Society of Thoracic Surgeons

cardioplegia (BC) delivered both anterograde and retrograde according to the Buckberg[2] protocol. However, the need for coronary sinus catheter placement, frequent redosing, high solution volume, and difficult intraoperative glucose management result in this strategy being cumbersome in the clinical setting. Del Nido cardioplegia (DC)[3] has a proven safety track record in pediatric cardiac surgery with single-dose administration for more than 90 minutes of cardioplegic arrest.[4] Some adult centers have adopted DC for reoperative aortic valve,[5] postinfarction coronary artery bypass,[6] and isolated valve[7] surgeries with encouraging results. We have previously reported our initial experience with 100 patients undergoing isolated coronary artery bypass grafting (CABG)[8] operated with DC and described the advantages of DC in minimally invasive aortic valve surgery.[9] A recent small randomized trial[10] in valve and CABG patients revealed equivalent clinical outcomes and myocardial protection with DC versus BC, corroborating previous data and providing impetus for further investigation. The current study was undertaken to evaluate myocardial protection and clinical outcomes in patients undergoing isolated CABG using DC and BC in a large real-world patient cohort.

METHODS

This study was approved by our institutional review board and was in full compliance with its policies and procedures. We performed a retrospective review of the clinical outcomes of all consecutive patients undergoing isolated CABG operated by the 2 study surgeons (T.A.T., C.L.W.) from January 2012 to October 2017. During this time interval, a total of 851 consecutive isolated CABG surgeries were performed at our center by the 2 study surgeons. BC was used in 350 patients from January 2012 to April 2014 and DC was used in 501 patients from May 2014 to October 2017. Although consecutive series introduce a time bias, surgical technique remained constant, and perioperative care was protocol driven and unchanged across the study period. Only one type of cardioplegia was used in each time phase of the study as the change from BC to DC was made in May 2014, thus limiting selection bias. Emergent and re-sternotomy operations were included, and there were no exclusion criteria.

DC was delivered in anterograde fashion in a 1:4 dilution with blood predominantly as a single dose of 1000 mL at 4°C. DC re-dosing was planned at 60 minutes from the initial dose if total aortic crossclamp time was anticipated to exceed 90 minutes. Myocardial temperature was not measured, and no topical hypothermia was used. BC was administered in a 4:1 blood dilution and given as initial anterograde and/or retrograde bolus of 1000 to 2000 mL at 4°C to achieve a myocardial temperature of less than 10°C. Subsequently, anterograde or retrograde delivery was repeated every 15 to 20 minutes and monitored by myocardial temperature in most cases. A 500-cc "warm shot" of warm blood only was delivered retrograde in majority of cases pending surgeon preference. Systemic hypothermia was not used routinely in either group, and body temperature was allowed to drift during the procedure.

Volume and mode of cardioplegia delivered and intraoperative hemoglobin levels were obtained from the electronic perfusion record. Level of inotropic support before leaving the operating room was recorded from the patient's electronic medical record. Troponin T levels were drawn on all patients 16 hours after surgery in accordance with temporal peak troponin T levels in patients with myocardial infarction.[11] Preoperative clinical characteristics, perioperative mortality, and 30-day events were queried directly from the Society of Thoracic Surgeons (STS) database. Distant mortality data were obtained from the Michigan State Social Security Death Index. Available postoperative echocardiographic studies for assessment of left ventricular (LV) function were retrieved from the electronic medical record. Quality of myocardial protection as characterized by postoperative troponin T levels and echocardiographically determined ejection fraction represented the primary outcome while 30-day and distant mortality represented secondary outcomes.

Statistical Methods

Descriptive statistics were used to summarize demographics and pre- and postoperative variables. If a variable was normally distributed and continuous, then mean ± standard deviation was used; otherwise, median [interquartile range] was used. For variables that were categorical, count (percent) was used. All the continuous univariate analyses were completed using a 2-sample t test or a Wilcoxon rank-sum test depending on if normality assumption was met and the categorical analysis with χ^2 unless the cells with expected counts less than 5 exceed 20% then Fisher exact test was used. Propensity matching was performed using logistic regression and a greedy 1:1 match starting with the fifth decimal place of the probability. The variables we included for the propensity matching were peripheral arterial disease, cerebral vascular disease, body mass index, previous myocardial infarction, status, sex, and age. When the propensity match completed, we were left with a total of 650 patients (325 per group). Side-by-side overlay histograms were created to show the distribution of the propensity probabilities in the unmatched and propensity matching group (Figure E1). Subgroup analyses were done on 4 different groups: age greater than or equal to 75 years, left ventricular ejection fraction (LVEF) less than or equal to 35%, presence of left main disease, and STS score greater than or equal to 2.5%. Each subgroup was then propensity matched with the same technique and variables as the overall cohort. A standard mean difference (also known as a z score) was used in place of P values for demographic and preoperative variable comparisons across groups. This was done to account for differences in sample sizes. The z score gives the number of standard deviations above or below the mean, with those with a value below –1.96 or above 1.96 considered to be statistically significant for a 2-sided test and one can reasonably reject the null hypothesis. Kaplan–Meier curves and a log rank test statistic were generated from survival data to determine whether there was a difference in survival probability over 4 years. Level of statistical significance was set at $P < .05$.

RESULTS

Table 1 summarizes the preoperative characteristics of the 2 patient groups after propensity matching. In the propensity-matched cohorts, the mean STS score was 1.37 ± 1.74% and 1.91 ± 3.14% for patients receiving BC and DC, respectively. Greater number of bypass grafts were performed in the propensity-matched patients receiving BC. Pertinent intraoperative data are presented

TABLE 1. Preoperative characteristics

	Unmatched				Propensity-matched			
	Missing	BC (n = 350)	DC (n = 501)	z value	Missing	BC (n = 325)	DC (n = 325)	z value
Age, y	0	65 ± 10	66 ± 10	–1.71	0	65 ± 10	66 ± 11	–0.17
Male	0	277 (79)	387 (77)	0.66	0	260 (80)	258 (79)	0.19
Diabetes	1	150 (43)	215 (43)	0.04	0	138 (42)	135 (41)	0.24
CVA	1	19 (5.4)	34 (6.8)	0.81	0	18 (5.5)	15 (4.6)	0.54
MI	1	133 (38)	229 (46)	2.26	0	129 (40)	136 (42)	0.56
PAD	1	49 (14)	56 (11)	1.22	0	41 (13)	39 (12)	0.24
CVD	1	39 (11)	103 (21)	3.64	0	38 (12)	41 (13)	0.36
HTN	1	310 (89)	443 (89)	0.01	0	287 (88)	283 (87)	0.48
Dialysis	1	9 (2.6)	8 (1.6)	1.00	0	8 (2.5)	8 (2.5)	0.00
Status								
Elective	0	189 (54)	255 (51)	2.33	0	168 (52)	174 (53)	2.11
Urgent		158 (45)	230 (46)			154 (47)	141 (43)	
Emergent		3 (0.9)	16 (3.2)			3 (0.9)	10 (3.1)	
IABP	1	23 (6.6)	48 (9.6)	1.57	1	23 (7.1)	31 (10)	1.15
Cardiogenic shock	2	5 (1.4)	10 (2.0)	0.63	1	5 (1.5)	4 (1.2)	0.33
Reoperation	31	3 (0.9)	11 (2.3)	1.62	0	3 (0.9)	8 (2.5)	1.52
Preoperative creatinine, mg/dL	3	0.99 [0.86-1.17]	1.02 [0.87-1.20]	–1.18	1	0.99 [0.87-1.18]	1.02 [0.88-1.21]	1.27
LVEF (%)	18	53 ± 12	52 ± 12	0.29	12	53 ± 12	52 ± 12	0.87
Number of grafts	1	3 [3-4]	3 [3-4]	3.35	1	3 [3-4]	3 [3-4]	–3.18
BMI, kg/m^2	103	31.0 ± 5.7	30.3 ± 5.5	1.70	0	30.5 ± 5.4	30.6 ± 5.5	–0.38
STS score, %	1	0.82 [0.51-1.46]	1.05 [0.58-1.92]	–3.54	1	0.84 [0.52-1.46]	0.99 [0.52-1.82]	1.71

Normally distributed data expressed as mean ± standard deviation and non-normal data expressed as median [interquartile range, 25th-75th]. Categorical variables are represented as count (percent). *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CVA*, cerebral vascular accident; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *CVD*, cerebral vascular disease, *HTN*, hypertension; *IABP*, intra-aortic balloon pump; *LVEF*, left ventricular ejection fraction; *BMI*, body mass index; *STS*, Society of Thoracic Surgeons.

in Table 2. DC solution was delivered anterograde in 98.6% (494/501) of patients, retrograde in 0.2% (1/501), and both in 1.2% (6/501). BC was delivered both antero- and retrograde in 62.6% (219/350) patients, anterograde in 36.9% (129/350), and retrograde in 0.6% (2/350). Patients receiving BC received greater volume and multiple doses of cardioplegia, whereas 83% (417/501) of patients receiving DC received a single dose for the entire operative procedure. Cardiopulmonary bypass and aortic crossclamp times were lower in patients receiving DC. All patients were routinely weaned from cardiopulmonary bypass with norepinephrine and milrinone as per standard protocol, with statistically greater levels of norepinephrine and milrinone support observed in patients receiving BC (Table 2), although the clinical significance of this finding is unclear. Postoperative outcomes are presented in Table 3. Thirty-day

TABLE 2. Intraoperative data

	Unmatched			Propensity-matched			
	Missing	BC (n = 350)	DC (n = 501)	Missing	BC (n = 325)	DC (n = 325)	*P* value
Cardioplegia volume, mL	39	3565 [2600-4895]	1000 [650-1100]	32	3620 [2625-4906]	1000 [650-1095]	<.01
Number of doses	19	5 [4-7]	1 [1-1]	12	5 [4-7]	1.0 [1.0-1.0]	<.01
CPB time, min	2	99 ± 29	86 ± 27	2	99 ± 28	85 ± 26	<.01
Aortic clamp time, min	3	81 ± 24	69 ± 20	3	82 ± 24	68 ± 20	<.01
Norepinephrine, μg/kg/min	58	0.04 [0.02-0.07]	0.03 [0.01-0.05]	54	0.04 [0.02-0.07]	0.04 [0.01-0.05]	<.01
Milrinone, μg/kg/min	59	0.20 [0.20-0.38]	0.20 [0.00-0.20]	54	0.20 [0.20-0.38]	0.20 [0.10-0.20]	<.01
Lowest hematocrit, %	2	25.6 ± 4.9	26.3 ± 5.1	2	25.6 ± 4.9	26.2 ± 5.0	.15

Normally distributed data expressed as mean ± standard deviation and non-normal data expressed as median [interquartile range, 25th-75th]. *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CPB*, cardiopulmonary bypass.

TABLE 3. Postoperative outcomes

	Unmatched			Propensity-matched			
	Missing	BC (n = 350)	DC (n = 501)	Missing	BC (n = 325)	DC (n = 325)	*P* value
Mortality, 30-d	0	2 (0.6)	3 (0.6)	0	2 (0.6)	2 (0.6)	1.00
CVA	0	4 (1.1)	7 (1.4)	0	4 (1.2)	5 (1.5)	1.00
Renal failure	0	12 (3.4)	12 (2.4)	0	12 (3.7)	6 (1.9)	.15
Atrial fibrillation	1	79 (23)	150 (30)	1	75 (23)	107 (33)	<.01
IABP	1	0 (0.0)	2 (0.4)	1	0 (0.0)	1 (0.3)	.50
Reoperation	0	1 (0.3)	4 (0.8)	0	1 (0.3)	4 (1.2)	.37
Prolonged intubation	0	18 (5.1)	26 (5.2)	0	16 (4.9)	17 (5.2)	.86
Surgical-site infection	102	9 (2.6)	7 (1.8)	0	7 (2.1)	6 (1.9)	.78
Blood products	1	108 (31)	149 (30)	0	101 (31)	108 (33)	.56
Creatinine, mg/dL	1	1.13 [0.96-1.49]	1.14 [0.93-1.50]	0	1.13 [0.97-1.49]	1.14 [0.95-1.51]	.78
LOS, d	1	7 [6-10]	8 [6-11]	0	7 [6-10]	8 [6-10]	.79

Categorical variables are represented as count (percent) and non-normal numeric data are expressed as median [interquartile range, 25th-75th]. *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CVA*, cerebral vascular accident; *IABP*, intra-aortic balloon pump; *LOS*, length of stay.

mortality was low in both groups and rate of postoperative complications similar. The incidence of atrial fibrillation was significantly greater in patients receiving DC, yet stroke rate and length of hospital stay did not differ between the 2 groups. Short-term survival data beyond 30 days are summarized in Figure 1. Survival of patients receiving BC and DC was similar up to 48 months postoperatively.

Assessment of Myocardial Protection

In propensity-matched patients, troponin T levels were lower in the patients receiving DC (0.46 [0.27-0.81] ng/mL vs 0.28 [0.16-0.59] ng/mL for BC and DC, respectively; $P < .01$). Distribution of troponin T levels in the matched patient populations is illustrated in Figure E2. For functional assessment of myocardial protection, postoperative transthoracic echocardiography was available on 151 of 325 (46.5%) patients receiving BC and 155 of 325 (44.5%) patients receiving DC. Mean echocardiographic follow-up was 27.9 ± 21.9 months and 12.9 ± 11.7 months for BC and DC, respectively ($P = .001$). The mean postoperative ejection fraction was 54 ± 12% for patients receiving BC and 53 ± 13% for patients receiving DC and did not differ significantly ($P = .36$). LV end-systolic (3.20 [2.90-3.70] cm vs 3.50 [2.90-4.30] cm; $P = .1$) and end-diastolic (4.60 [4.30-5.20] cm vs 4.80 [4.30-5.40] cm; $P = .19$) dimensions did not differ between BC and DC.

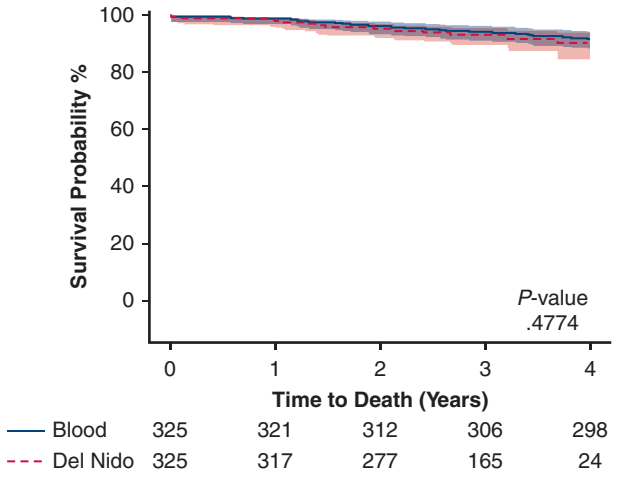


FIGURE 1. Kaplan–Meier survival curves for blood cardioplegia (*blue*) and del Nido cardioplegia (*red*) up to 4 years postoperatively in study population after propensity matching. *Shaded areas* represent confidence limits.

Subgroup Analysis

To evaluate the efficacy of DC versus BC in greater-risk patients undergoing CABG, postoperative troponin levels, myocardial performance, and clinical outcomes were compared in patients with advanced age (≥75 years), reduced myocardial function (LVEF ≤35%), greater that 50% left main disease, and STS score of greater or equal to 2.5%. For the patients with STS score ≥2.5%, the mean STS score was 4.69 ± 3.15% for BC and 7.03 ± 5.72% for DC. The results of the subgroup analyses are presented in Table 4 and demonstrate that DC provided noninferior myocardial protection and clinical outcomes to BC in these individual greater-risk patient cohorts. Troponin T level distributions in the analyzed subgroups are presented in Figures E3-E6. In our study, 72 (17%) patients in the DC group received a second dose of cardioplegia due to complexity of the operation or anticipated prolonged aortic cross-clamp time. When compared with the 350 patients in the BC group, this subset of patients receiving DC had a significantly greater rate of reoperative surgery (6.3% vs 0.9%) and cerebral vascular disease (5.4% vs 11.1%) (Table E1), and longer aortic crossclamp time (89 ± 24 minutes vs 81 ± 24 minutes) (Table E2). However, the postoperative troponin level

TABLE 4. Propensity-matched subgroup analysis

	Age ≥75 y			LVEF ≤35%			Left main disease			STS risk score ≥2.5%		
	BC (n = 62)	DC (n = 62)	*P* value	BC (n = 38)	DC (n = 38)	*P* value	BC (n = 73)	DC (n = 73)	*P* value	BC (n = 41)	DC (n = 41)	*P* value
Troponin T, ng/mL	0.52 [0.34-0.88]	0.34 [0.23-0.73]	.10	0.38 [0.23-0.75]	0.53 [0.23-0.90]	.69	0.47 [0.28-0.84]	0.29 [0.17- 0.55]	.004	0.58 [0.35-1.64]	0.62 [0.23-0.99]	.25
Preoperative LVEF, %	53 ± 12	51 ± 14	.36	26 ± 7	30 ± 6	.06	53 ± 13	51 ± 13	.41	44 ± 15	43 ± 14	.74
Postoperative LVEF, %	52 ± 17	50 ± 14	.53	41 ± 14	43 ± 12	.58	54 ± 13	53 ± 13	.68	44 ± 14	47 ± 16	.47
Mortality, 30-d	0 (0.0)	1 (1.6)	1.00	0 (0.0)	0 (0.0)	NA	1 (1.4)	3 (4.1)	.62	1 (2.4)	1 (2.4)	1.00
Stroke	2 (3.2)	0 (0.0)	.50	1 (2.6)	2 (5.3)	1.00	0 (0.0)	0 (0.0)	NA	2 (4.9)	0 (0.0)	.49
Atrial fibrillation	26 (42)	26 (42)	1.00	12 (32)	17 (45)	.24	19 (26)	22 (30)	.58	13 (32)	22 (54)	.04
Renal failure	5 (8.1)	4 (6.5)	1.00	2 (5.3)	3 (7.9)	1.00	3 (4.1)	2 (2.7)	1.00	7 (17)	4 (10)	.33

Categorical variables are represented as count (percent) and non-normal numeric data are expressed as median [interquartile range, 25th-75th]. *LVEF*, Left ventricular ejection fraction; *STS*, Society of Thoracic Surgeons; *BC*, blood cardioplegia; *DC*, del Nido cardioplegia; *NA*, not available.

(0.45 [0.25-0.83] ng/mL and 0.46 [0.27-0.82] ng/mL) and LVEF (57 ± 12% and 54 ± 12%) did not different between DC and BC, although the rate of postoperative intra-aortic balloon pump use was greater in the DC group (2.8% [2/72] vs 0% [0/350]), as was the stroke rate (5.6 [4/72]% vs 1.1 [4/350]%) (Table E3). For the 11 reoperative patients in the DC group, the median postoperative troponin T was 0.25 [0.18-0.83] ng/mL and preoperative LVEF remained preserved (49 ± 8% and 47 ± 15%, for pre- and postoperative LVEF, respectively) (Tables E4-E6).

DISCUSSION

Safe and reliable myocardial protection is paramount in surgical procedures requiring cardiac standstill. The current study demonstrated noninferior myocardial protection and clinical outcomes with DC versus BC in both routine and greater-risk patients undergoing isolated CABG with relatively short aortic crossclamp times.

We have previously reported[8] our initial experience with DC in patients undergoing isolated CABG, demonstrating equivalent myocardial protection to BC and corroborating the study of Yerebakan and colleagues[6] in high-risk patients undergoing CABG. Equipoise of DC to BC has also been reported in routine isolated valve surgery,[7] reoperative aortic valve surgery,[5] minimally invasive aortic valve replacement,[9,12] and low-risk patients undergoing isolated CABG.[13] The first randomized trial comparing DC and BC in CABG and valve patients[10] was published recently and revealed equivalent clinical outcomes and myocardial protection corroborating our data. However, the number of patients in that study was low and reoperative and hemodynamically supported patients were excluded. The current study represents the largest real-world clinical experience for isolated coronary artery bypass surgery with all consecutive patients included over an almost 6-year study period. These data solidify our experience and confirm previous findings.[13] We found postoperative troponin levels to be lower in patients receiving DC than in patients receiving BC, even in light of a greater STS risk profile, although the clinical importance of this difference should not be overstated. A similar trend of lower troponin levels was observed in isolated aortic valve replacement[7] and randomized CABG and valve patients.[10] In our study, postoperative LV function was similar between the 2 myocardial protective strategies, consistent with comparable preservation of LV function with DC reported previously.[5,8,9] Thus, biochemical and functional markers of myocardial protection were very comparable between BC and DC in this large patient cohort. Lack of perioperative or 4-year mortality difference between BC and DC provides further support for similar efficacy. Recent molecular data suggest that lidocaine-based cardioplegia has the potential to induce genetic expression that favors myocardial preservation,[14] possibly providing novel mechanistic support for these clinical findings.

Clinical outcomes were similar between BC and DC except for subset of patients receiving DC requiring more than 1 cardioplegia dose who demonstrated greater stroke rates in an unmatched analysis. Atrial fibrillation in the propensity-matched patient groups was greater in the DC group. Salinas and colleagues[13] reported equivalent clinical outcomes in 408 consecutive patients undergoing isolated CABG operated using either BC or DC with postoperative atrial fibrillation rate of 22% in each group. However, these were low-risk patients with a mean STS score of 0.95% and 1.1% for BC and DC, respectively. The STS benchmark for postoperative atrial fibrillation for patients undergoing isolated CABG in 2016 was 24.9%[15]; thus, our observed

difference may be due to a relatively low rate of this complication in the BC group and the significantly greater STS score of our patients receiving DC. In greater-risk cohorts and in patients with STS score ≥2.5%, the rate of postoperative atrial fibrillation was similar in the 2 groups.

Use of DC in multivessel CABG surgery has raised concerns for suboptimal distribution of cardioplegic solution,[16] particularly with anterograde delivery or in the setting of left main disease. Our data revealed postoperative troponin levels and myocardial function to be similar between BC and DC for the entire study population and for selected high-risk cohorts, partially alleviating these fears. Neither topical nor systemic hypothermia were used as cardioprotective adjuncts, as suggested by others.[10] Similar clinical outcomes with BC and DC for high-risk patients with acute myocardial infarction undergoing CABG were reported by the Columbia group,[6] but the study did not include postoperative troponin levels or assessment of myocardial function and was hampered by low patient numbers. In our study, we found DC to provide noninferior myocardial protection and clinical results in 41 patients with a mean STS score of 7%, hence justifying its use in greater composite risk patient cohorts. However, the number of patients in our subgroups was relatively small, and a larger experience is needed to confirm these results.

Use of DC was associated with reduced aortic crossclamp time, and although some of this difference may be attributable to most patients receiving BC receiving a "hot shot" before clamp removal and fewer distal anastomoses, simplification of the cardioplegic regimen may also contribute. In minimally invasive aortic valve surgery, DC has been associated with shorter aortic crossclamp times,[9,12] but this may be due to the simplicity of single anterograde dose administration in a limited surgical field. Randomized data[10] have not shown decreased ischemic times with DC versus BC. Whether our observed time savings have clinical significance is unclear, but the use of DC enhanced the "flow" of the procedure by eliminating undue interruptions. Although DC can be delivered retrograde, we found anterograde delivery reliable, facilitating a tidy operative filed while permitting expeditious performance of the planned procedure.

Single-dose administration of DC for aortic crossclamping of 90 minutes has been well accepted in the pediatric literature,[4] but ventricular hypertrophy and coronary artery disease typical of the adult population may affect delivery and distribution of cardioplegic solution. Indeed, the inventor of the solution has voiced reservations regarding its use in adult surgery.[17] The feasibility of single-dose DC has previously been reported in smaller studies[6,8,9] and is supported for isolated CABG by the current data, as 83% of

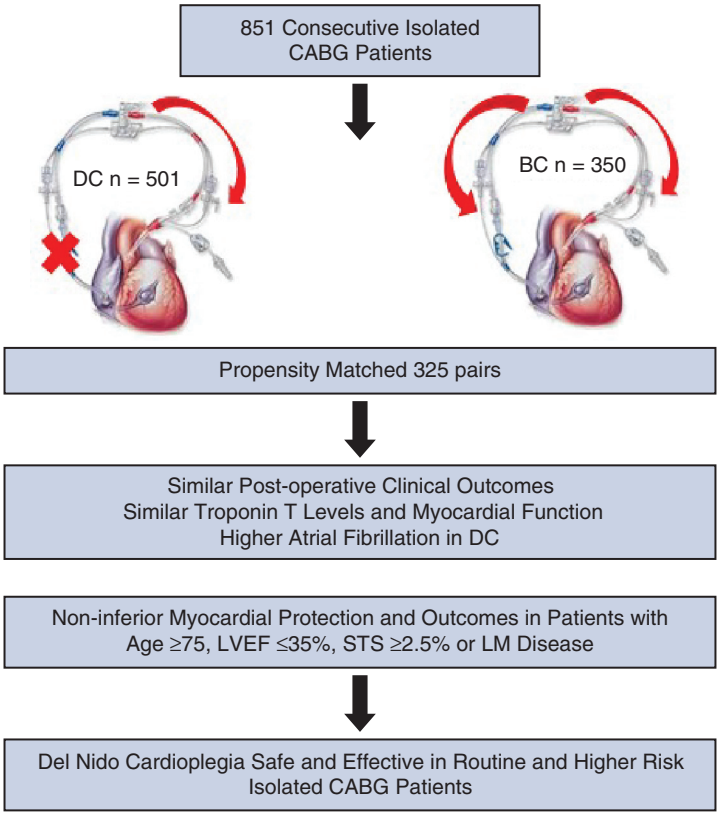


FIGURE 2. Summary of study design and clinical outcomes. *CABG*, Coronary artery bypass grafting; *DC*, del Nido cardioplegia; *BC*, blood cardioplegia; *LVEF*, left ventricular ejection fraction; *STS*, Society of Thoracic Surgeons; *LM*, left main coronary artery.

patients receiving DC in the study received only a single dose of cardioplegia. Experimentally, superior myocardial function recovery has been reported with single versus multidose DC for a 60-minute cardioplegic arrest in an isolated rat heart.[18] However, it is imperative that DC be re-dosed for longer and more complex surgeries under a predetermined protocol to avoid a re-dosing ''time creep'' that may cumulate in inadequate myocardial protection.

As summarized in Figure 2, our clinical series of 851 consecutive patients undergoing isolated CABG yielded a propensity-matched analysis of 325 patient pairs receiving either DC or BC as myocardial protective strategy during surgical coronary revascularization. Our data demonstrated that DC provided noninferior myocardial protection, clinical outcomes, and short-term survival to BC. DC demonstrated feasibility of single-dose administration for routine and greater-risk patients undergoing CABG, but for longer, more complex cardiac procedures, optimal dosing and delivery of DC remains to be established. These data warrant larger randomized studies to further explore the safety and efficacy of DC in adult cardiac surgery.

Limitations

The results of this clinical study must be interpreted in light of several important limitations. This was a single-center study, and extrapolation of these results must be interpreted in that context. As we did not randomize the patients to the respective cardioplegia groups, there is an inherent selection bias in the study design, which we attempted to minimize by including all consecutive patients operated by the 2 study surgeons during the study period. Furthermore, the surgeons in the study were dedicated to only one cardioplegic solution during each phase of the study, thus limiting the ability to alternate between solutions. This was not a concurrent series and the effect of changes/advances in surgical care over the 6-year study period on operative outcomes may be considered. However, our center relies heavily on standardized protocols that were not altered for the purpose of this study, and as such, we believe the temporal influence on our data is negligible. Most patients in the study had normal preoperative myocardial performance and were considered to be of routine risk; however, emergent, re-sternotomy, and low LVEF patients were included in this consecutive series, providing an ''all-comer'' real-world experience. Extrapolation of DC efficacy from these patients undergoing isolated CABG with relatively short aortic crossclamp time to complex cardiac cases requiring prolonged aortic crossclamping may require adjustment of dose, mode of delivery, and dosing intervals and should be performed with caution.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

1. Sa MP, Rueda FG, Ferraz PE, Chalegre ST, Vasconcelos FP, Lima RC. Is there any difference between blood and crystalloid cardioplegia for myocardial protection during cardiac surgery? A meta-analysis of 5576 patients from 36 randomized trials. *Perfusion*. 2012;27:535-46.
2. Folette DM, Fey K, Buckberg GD, Helly JJ Jr, Steed DL, Foglia RP, et al. Reducing postischemic damage by temporary modification of reperfusate calcium, potassium, pH, and osmolarity. *J Thorac Cardiovasc Surg*. 1981;82:221-38.
3. Matte GS, del Nido PJ. History and use of del Nido cardioplegia solution at Boston's Childrens's Hospital. *J Extra Corpor Technol*. 2012;44:98-103.
4. Charette K, Gerrah R, Quaegebeur J, Chen J, Riley D, Mongero L, et al. Single dose myocardial protection techniques utilizing del Nido cardioplegia solution during congenital heart surgery procedures. *Perfusion*. 2012;27:98-103.
5. Sorabella Ra, Akashi H, Yerebakan H, Najjar M, Mannan A, Williams MR, et al. Myocardial protection using del Nido cardioplegia solution in adult re-opertive aortic valve surgery. *J Card Surg*. 2014;29:445-9.
6. Yerebakan H, Sorabella RA, Najjar M, Castillero E, Mongero L, Beck J, et al. Del Nido cardioplegia can be safely administered in high risk coronary artery bypass grafting surgery after acute myocardial infarction: a propensity matched comparison. *J Cardiothorac Surg*. 2014;9:141.
7. Mick SL, Robich MP, Houghtaling PL, Gillinov AM, Soltesz EG, Johnston DR, et al. Del Nido versus Buckberg cardioplegia in adult isolated valve surgery. *J Thorac Cardiovasc Surg*. 2015;149:626-36.
8. Timek T, Willekes C, Hulme O, Himelhoch B, Nadeau D, Borgman A, et al. Propensity matched analysis of del Nido cardioplegia in adult coronary artery bypass grafting: initial experience with 100 consecutive patients. *Ann Thorac Surg*. 2016;101:2237-41.
9. Ziazadeh D, Mater R, Himelhoch B, Borgman A, Parker JL, Willekes CL, et al. Single-dose del Nido cardioplegia in minimally invasive aortic valve surgery. *Semin Thorac Cardiovasc Surg*. Nov 2, 2017 [Epub ahead of print].
10. Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM, Fitzgerald D. The use of del Nido cardioplegia in adult cardiac surgery: a prospective randomized trial. *J Thorac Cardiovasc Surg*. 2018;155:1011-8.
11. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndrome. *Clin Chem*. 2007;53:552-74.
12. Vistarini N, Laliberté E, Beauchamp P, Bouhout I, Lamarche Y, Cartier R, et al. Del Nido cardioplegia in the setting of minimally invasive aortic valve surgery. *Perfusion*. 2017;32:112-7.
13. Salinas GE, Nutt R, Rodriguez-Araujo G. Del Nido cardioplegia in low risk adults undergoing first time coronary artery bypass surgery. *Perfusion*. 2017;32:68-73.
14. Heydarpour M, Ejiofor J, Gilfeather M, Stone G, Gorham J, Seidman CE, et al. Molecular genetics of lidocaine-containing cardioplegia in the human heart during cardiac surgery. *Ann Thorac Surg*. 2018;106:1379-80.
15. Badhwar V, Rankin JS, Thourani VH, D'Agostino RS, Habib RH, Shahian DM, et al. The Society of Thoracic Surgeons adult cardiac surgery database: 2018 update on research: outcomes analysis, quality improvement, and patient safety. *Ann Thorac Surg*. 2018;106:8-13.
16. Kim K, Ball C, Grady P, Mick S. Use of del Nido cardioplegia for adult cardiac surgery at the Cleveland Clinic: perfusion implications. *J Extra Corporeal Technol*. 2014;46:317-23.
17. Invited commentary. Del Nido PJ. *Ann Thorac Surg*. 2016;101:2241-2.
18. Govindapillai A, Friesen CH, O'Blenes SB. Protecting the aged heart during cardiac surgery: single-dose del Nido cardioplegia is superior to multi-dose del Nido cardioplegia in isolated rat hearts. *Perfusion*. 2016;31:135-42.

Key Words: coronary artery bypass surgery, cardioplegia

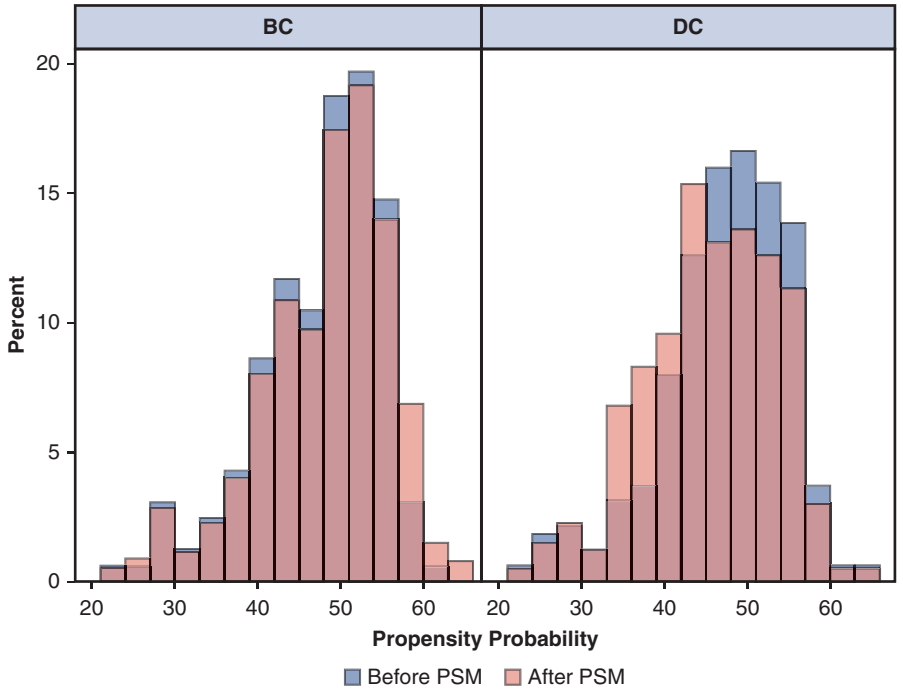


FIGURE E1. Propensity score matching probabilities mirrored by cardioplegia. The *dark red* in the figure denotes an overlay in the before and after histograms. *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *PSM*, propensity score matching.

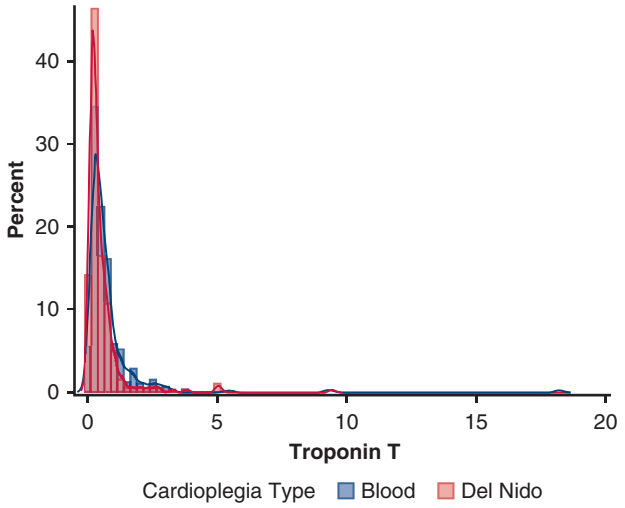


FIGURE E2. Troponin T distribution for all propensity-matched patients.

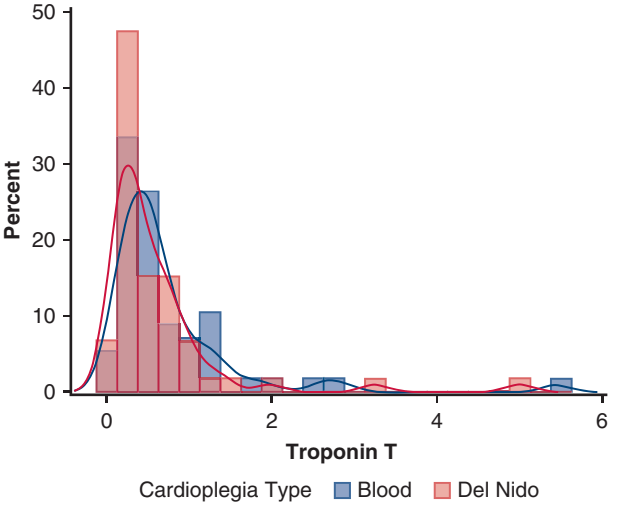


FIGURE E3. Troponin T distribution for patients age 75 or greater.

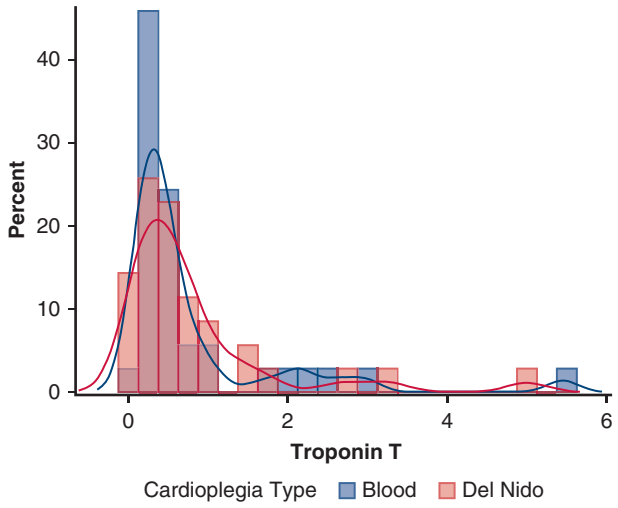


FIGURE E4. Troponin T distribution for patients with left ventricular ejection fraction of 35% or less.

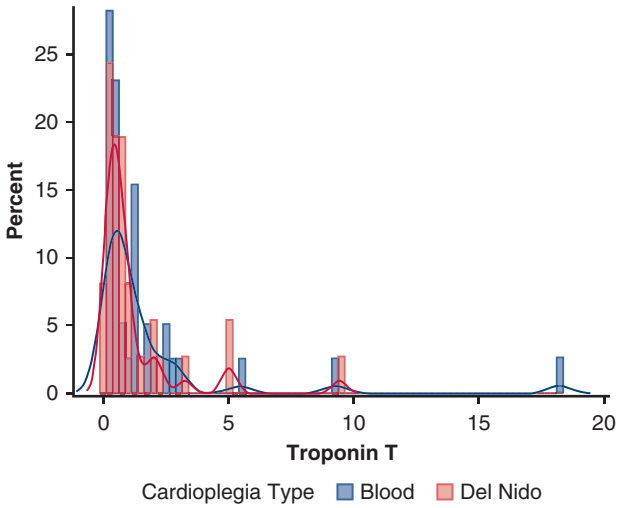


FIGURE E6. Troponin T distribution of patients with Society of Thoracic Surgeons score of 2.5% or greater.

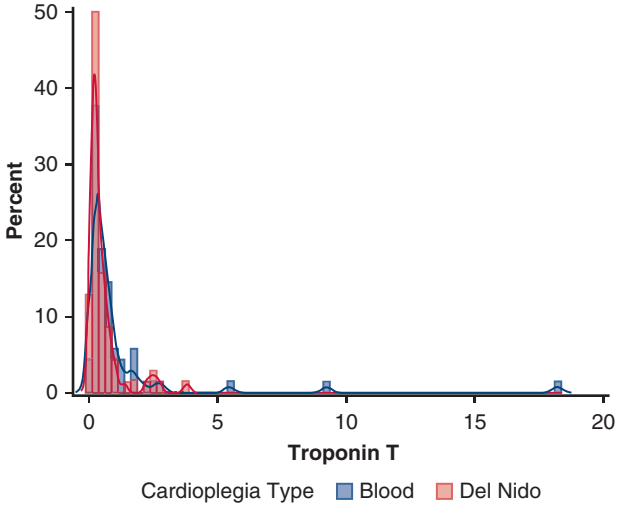


FIGURE E5. Troponin T distribution for patients with left main disease.

TABLE E1. Preoperative characteristics BC versus DC with more than 1 dose

	Missing	BC (n = 350)	DC 1 + dose (n = 72)	*P* value
Age, y	0	65 ± 10	63 ± 11	.29
Male	0	277 (79)	56 (78)	.80
Diabetes	0	150 (43)	31 (43)	.98
CVA	0	19 (5.4)	8 (11)	.11
MI	0	133 (38)	36 (50)	.06
PAD	0	49 (14)	8 (11)	.51
CVD	0	39 (11)	14 (19)	.05
HTN	0	310 (89)	61 (85)	.36
Dialysis	0	9 (2.6)	1 (1.4)	1.00
Status Elective Urgent Emergent	0	 189 (54) 158 (45) 3 (0.9)	 38 (53) 32 (44) 2 (2.8)	.36
IABP	0	23 (6.6)	9 (12)	.08
Cardiogenic shock	0	5 (1.4)	1 (1.4)	1.00
Reoperation	9	3 (0.9)	4 (6.3)	.01
Preop creatinine, mg/dL	0	0.99 [0.86-1.17]	1.03 [0.89-1.19]	.36
LVEF, %	6	53 ± 12	55 ± 10	.20
Number of grafts	0	3 [3-4]	4 [3-4]	.07
BMI, kg/m^2	20	31.0 ± 5.7	30.2 ± 5.3	.40
STS score, %	0	0.82 [0.51-1.46]	0.98 [0.60-1.47]	.29

Normally distributed data expressed as mean ± standard deviation and non-normal data expressed as median [interquartile range, 25th-75th]. Categorical variables are represented as count (percent). *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CVA*, cerebral vascular accident; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *CVD*, cerebral vascular disease; *HTN*, hypertension; *IABP*, intra-aortic balloon pump; *LVEF*, left ventricular ejection fraction; *BMI*, body mass index; *STS*, Society of Thoracic Surgeons.

TABLE E2. Intraoperative BC versus DC with more than 1 dose

	Missing	BC (n = 350)	DC 1+ dose (n = 72)	*P* value
Cardioplegia volume, mL	31	3565 [2600-4895]	1444 [1013-1675]	<.01
Number of doses	11	5 [4-7]	2 [2-2]	<.01
CPB time, min	0	99 ± 29	115 ± 33	<.01
Aortic clamp time, min	0	81 ± 24	89 ± 24	.01
Norepinephrine, μg/kg/min	58	0.04 [0.02-0.07]	0.04 [0.01-0.06]	.02
Milrinone, μg/kg/min	58	0.20 [0.20-0.38]	0.20 [0.00-0.20]	<.01
Lowest hematocrit, %	0	25.6 ± 4.9	26.1 ± 4.7	.49

Normally distributed data expressed as mean ± standard deviation and non-normal data expressed as median [interquartile range, 25th-75th]. *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CPB*, cardiopulmonary bypass.

TABLE E3. Postoperative outcomes BC versus DC with more than 1 dose

	Missing	BC (n = 350)	DC 1+ dose (n = 72)	*P* value
Mortality, 30-d	0	2 (0.6)	1 (1.4)	.43
CVA	0	4 (1.1)	4 (5.6)	.03
Renal failure	0	12 (3.4)	1 (1.4)	.70
Atrial fibrillation	0	79 (23)	23 (32)	.09
IABP	0	0 (0.0)	2 (2.8)	.03
Reoperation	0	1 (0.3)	1 (1.4)	.31
Prolonged intubation	0	18 (5.1)	5 (6.9)	.57
Surgical-site infection	20	9 (2.6)	0 (0.0)	.61
Blood products	0	108 (31)	30 (42)	.08
Creatinine, mg/dL	0	1.13 [0.96-1.49]	1.08 [0.93-1.37]	.31
LOS, d	0	7 [6-10]	7 [6-9]	.50
Troponin, ng/mL	19	0.46 [0.27-0.82]	0.45 [0.25-0.83]	.64
Last LVEF (%)	233	54 ± 12	57 ± 11	.21

Categorical variables are represented as count (percent) and non-normal numeric data are expressed as median [interquartile range, 25th-75th]. *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CVA*, cerebral vascular accident; *IABP*, intra-aortic balloon pump; *LOS*, length of stay; *LVEF*, left ventricular ejection fraction.

TABLE E4. Preoperative characteristics

	DC reoperations (N = 11)
Age, y	70 ± 10
Male	11 (100)
Diabetes	9 (82)
CVA	2 (18)
MI	5 (45)
PAD	2 (18)
CVD	2 (18)
HTN	9 (82)
Dialysis	0 (0)
Status	
Elective	6 (55)
Urgent	5 (45)
Emergent	0 (0.0)
IABP	1 (9.1)
Cardiogenic shock	0 (0.0)
Preoperative creatinine, mg/dL	1.01 [0.90-1.15]
LVEF, %	49 ± 8
Number of grafts	3 [3-3]
BMI, kg/m^2	30.5 ± 4.0
STS score, %	2.44 [1.07-3.66]

There were no missing values from this table. Normally distributed data expressed as mean ± standard deviation and non-normal data expressed as median [interquartile range, 25th-75th]. Categorical variables are represented as count (percent). *BC*, Blood cardioplegia; *DC*, del Nido cardioplegia; *CVA*, cerebral vascular accident; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *CVD*, cerebral vascular disease;*HTN*, hypertension; *IABP*, intra-aortic balloon pump; *LVEF*, left ventricular ejection fraction; *BMI*, body mass index; *STS*, Society of Thoracic Surgeons.

TABLE E5. Intraoperative data

	DC reoperations (N = 11)
Cardioplegia volume, mL	1150 [1000-2000]
CPB time, min	129 ± 51
Aortic clamp time, min	94 ± 31
Norepinephrine, μg/kg/min	0.04 [0.02-0.08]
Milrinone, μg/kg/min	0.20 [0.20-0.30]
Lowest hematocrit, %	24.6 ± 6.5

There were no missing values from this table. Normally distributed data expressed as mean ± standard deviation and non-normal data expressed as median [interquartile range, 25th-75th]. *DC*, Del Nido cardioplegia; *CPB*, cardiopulmonary bypass.

TABLE E6. Postoperative outcomes

	Missing	DC reoperations (N = 11)
Mortality, 30-d	0	0 (0.0)
CVA	0	0 (0.0)
Renal failure	0	1 (9.1)
Atrial fibrillation	0	5 (45)
IABP	0	0 (0.0)
Reoperation	0	0 (0.0)
Prolonged intubation	0	1 (9.1)
Surgical-site infection	0	1 (9.1)
Blood products	0	4 (36)
Creatinine, mg/dL	0	1.14 [0.94-1.82]
LOS, d	0	12 [7-20]
Troponin, ng/mL	2	0.25 [0.18-0.83]
Last LVEF, %	4	47 ± 15

Categorical variables are represented as count (percent) and non-normal numeric data are expressed as median [interquartile range, 25th-75th]. *DC*, Del Nido cardioplegia; *CVA*, cerebral vascular accident; *IABP*, intra-aortic balloon pump; *LOS*, length of stay; *LVEF*, left ventricular ejection fraction.